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Influence of acute and chronic alcohol intake on the clinical course and outcome in acetaminophen overdose

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SUMMARY

Background: Animal studies on acetaminophen toxicity suggest that chronic alcohol intake affects the outcome adversely, whereas acute alcohol intake seems protective. Few clinical data are available.

Methods: We studied 209 consecutive patients with single-dose acetaminophen overdose. The combined influence of independent variables (gender, age, dose, delay to antidote treatment, chronic and acute alcohol intake and nomogram risk group) on dependent variables (death, development of hepatic encephalopathy and biochemical liver markers) was studied using multiple or logistic regression analysis.

Results: Fifty-seven (27.3%) patients had chronic alcohol intake and 45 (21.5%) patients had acute alcohol intake. Forty-four (21.1%) patients developed hepatic coma and 20 (43.5%) of these patients died. Chronic alcohol intake was significantly and independently associated with the development of hepatic coma, with a lower prothrombin index, lower platelet count, higher creatinine and higher bilirubin. The relative risks for hepatic coma and death were 5.3 (95% confidence interval, 2.2–12.4) and 1.4 (95% confidence interval, 0.5–3.9), respectively, in the chronic alcohol intake group compared with the no chronic alcohol intake group. Acute alcohol intake was not significantly associated with any of the dependent variables studied.

Conclusions: Chronic alcohol intake enhances acetaminophen hepatotoxicity, whereas acute alcohol intake does not affect the clinical course.

INTRODUCTION

Acetaminophen (paracetamol) intoxication is a common cause of severe drug-induced hepatotoxicity and the leading cause of acute liver failure in Northern Europe,[1] the UK[2] and the USA.[3] While immediate antidote treatment is of paramount importance in all cases,[4] the identification of specific subgroups with increased risk of hepatotoxicity is necessary to achieve further improvements in treatment strategies and patient allocation. Because concomitant chronic or acute alcohol consumption is not uncommon in acetaminophen overdose,[5] it is relevant to examine the effect of alcohol intake in this clinical setting.

Animal studies on acetaminophen toxicity have reported that chronic alcohol intake increases mortality.[6] Morbidity is also increased, as indicated by higher aminotransferase levels,[7, 8] lower median lethal dose (LD_{50})[6, 9] and decreased hepatic glutathione levels[8] compared with animals without chronic alcohol intake. Acute alcohol intake, on the other hand, seems to have a hepatoprotective effect.[7, 10–13]

Clinical data on the possible interaction between alcohol intake and acetaminophen are sparse and mainly in the form of case reports.[14–17] A recent

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retrospective study demonstrated a higher proportion of chronic alcoholics in hospitalized patients with accidental acetaminophen overdose compared with intentional overdose.[5] The accidental group comprised a higher proportion of patients who had hepatotoxicity (defined as transaminase levels of 1000 U/L or higher) and who developed hepatic encephalopathy. To what extent chronic alcoholism contributed to the increased morbidity is unclear.[18] Another retrospective study on acetaminophen-induced acute liver failure reported a higher mortality rate among 30 patients with a daily alcohol intake above the recommendations of the Royal College of Physicians, compared with 49 non-drinkers (67% vs. 34%).[19] However, no correction for interaction with other variables, such as acetaminophen dose, acute alcohol intake and delay to antidote, was performed. In apparent contrast, a recent retrospective study from the same centre, including 553 patients with acetaminophen overdose, found no correlation between alcohol consumption and severity of hepatotoxicity,[20] but possible interactions between alcohol and other prognostic factors were not taken into account.

The aim of this study was to determine the independent influence of chronic and acute alcohol intake on the clinical course in 209 patients with acetaminophen intoxication, when adjusting for the influence of other variables using multivariate statistical analysis.

PATIENTS AND METHODS

We studied 209 consecutive patients (64 men, 145 women) with single-dose acetaminophen overdose admitted during a 30-month period (1993–1996) to the Liver Unit, Rigshospitalet, Copenhagen, Denmark. Criteria for admission to the Liver Unit included one or more of the following: hepatic encephalopathy and/or a prothrombin index < 0.40 [international normalized ratio (INR) > 1.5] and/or a serum creatinine level > 300 μmol/L. The study design was both retrospective (12 months) and prospective (18 months). Patients with multiple overdosage (over hours to days) were not included, because the time from overdose to antidote treatment is an important variable in assessing the prognosis.[21]

The patients were treated according to the Danish recommendations.[22] Thus, all patients received intravenous *N*-acetylcysteine treatment immediately at the first hospital admission. *N*-Acetylcysteine infusion was continued for at least 36 h and was only discontinued in the case of unequivocal signs of hepatic recovery (no hepatic encephalopathy and increase in the prothrombin index (decrease in INR) in three consecutive samples at least 6 h apart), or in the case of death. Patients with hepatic encephalopathy were treated according to standard guidelines.[23, 24]

Chronic alcohol intake was defined as ingestion of ≥ 50 g of ethanol per day for at least 3 months. Acute alcohol intake was defined as the intake of ≥ 50 g of ethanol taken within 2 h of the time of acetaminophen ingestion.

The history of alcohol intake was obtained from the patient by thorough interrogation, and from their next of kin. In case of doubt, the patient's general practitioner was also asked.

The influence of the following independent variables was studied: gender, age, acetaminophen dose, the delay from acetaminophen ingestion to the start of *N*-acetylcysteine treatment ('delay to *N*-acetylcysteine'), chronic alcohol intake, acute alcohol intake and nomogram risk group (high risk, intermediate risk and low risk of hepatotoxicity).[25, 26] To use this nomogram, the time from overdose vs. plasma acetaminophen concentration was plotted, where the lines indicate low, intermediate and high risk of hepatotoxicity.[26]

The impact of the independent variables on the following dependent variables was studied: development of hepatic encephalopathy (defined as grade II or more), death and the following biochemical variables: minimum prothrombin index (i.e. the biological activity of plasma coagulation factors II, VII and X), maximum alanine aminotransferase, minimum platelet count, maximum serum creatinine and, where possible, acidosis (arterial pH < 7.30) on admission.

Statistics

Variables were summarized as the median (and range) or percentage. The Mann–Whitney and chi-squared tests were used for univariate analyses for continuous and categorical data, respectively. The independent association of descriptive non-hepatological variables (chronic/acute alcohol intake, gender, age, delay to *N*-acetylcysteine, acetaminophen dose, nomogram risk group) on admission with the occurrence of hepatic encephalopathy (a) or death (b) was analysed using logistic regression analysis. The independent association of descriptive non-hepatological variables on admission with the minimum prothrombin index (c), maximum

alanine aminotransferase (d), minimum platelet count (e), maximum serum creatinine (f) and maximum serum bilirubin (g), respectively, was analysed using multiple regression analysis. The final models were obtained using the backward elimination technique. Variables were scored to fulfil the assumption of linearity. In some cases, a logarithmic transformation of variables was necessary. A 5% (two-sided) level of significance was used. From the obtained models, the adjusted influence of chronic alcohol intake on each of the above-mentioned variables (a–g) was calculated with 95% confidence limits using standard methodology.

RESULTS

Fifty-seven (27.3%) patients were identified in the chronic alcohol group and 45 (21.5%) patients in the acute alcohol group. Twenty-one patients fulfilled the criteria for both chronic and acute alcohol intake. In 40 patients with chronic alcohol intake, the median (range) daily ethanol consumption was 84 g (50–400 g). In 37 patients with acute alcohol intake, the median intake was 150 g (50–750 g). In 17 patients from the chronic alcohol group and in eight patients from the acute alcohol group, the exact alcohol intake above the threshold of 50 g ethanol could not be determined.

Forty-four (21.1%) patients developed hepatic encephalopathy grade II or more, fulfilling the criteria of acute liver failure,[24] and 20 (43.5%) of these patients died. No patients without encephalopathy died. Eleven patients were listed for liver transplantation; however, only two patients were transplanted.

Univariate analyses

Table 1 compares patients with and without chronic alcohol intake. The group with chronic alcohol intake were older, contained a higher proportion of men and individuals with acute alcohol intake, had taken a larger dose of acetaminophen and tended to start *N*-acetylcysteine treatment later than patients without chronic alcohol intake (Table 1). Many biochemical markers were more abnormal in patients with chronic alcohol intake than in those without. Hepatic encephalopathy was more prevalent in the chronic alcohol intake group, in which about 40% developed hepatic coma compared with less than 15% in the patients without chronic alcohol intake (Table 1). Mortality was higher in patients with chronic alcohol intake, but not significantly so.

The group with acute alcohol intake contained a larger proportion of men and of individuals with chronic alcohol intake (Table 1). Otherwise, patients with and without acute alcohol intake did not show significant differences with regard to the variables presented in Table 1.

Multivariate analyses

Logistic regression analyses showed that chronic alcohol intake and a long delay to antidote (*N*-acetylcysteine) treatment were independently associated with the occurrence of hepatic encephalopathy and acidosis on admission, respectively (Table 2). Patients who developed hepatic encephalopathy had a median delay to *N*-acetylcysteine of 44 h (range, 18–92 h).

The only independent risk factor associated with death was delay to *N*-acetylcysteine (Table 2). All patients who died had at least a 19-h delay to *N*-acetylcysteine (median, 36 h).

The results of the multiple regression analyses are presented in Table 3. The multiple regression models showed that chronic alcohol intake was independently associated with more abnormal extreme values of the prothrombin index, platelet count, serum creatinine and serum bilirubin, and tended to be associated with maximum alanine aminotransferase (Table 3). A delayed antidote (*N*-acetylcysteine) treatment was independently associated with more abnormal extreme values for the same variables (Table 3). A high acetaminophen dose was independently associated with a lower prothrombin index, lower platelet count and higher alanine aminotransferase. An older age was independently associated with a lower prothrombin index and a higher alanine aminotransferase, while female gender was independently associated with a higher bilirubin (Table 3).

Acute alcohol intake was not a significant independent variable in any of the multivariate models.

Table 4 summarizes the adjusted influence of chronic alcohol intake on the dependent variables studied in the multivariate models.

DISCUSSION

By multiple regression and logistic regression analyses, it was possible for the first time to evaluate the independent influence of chronic and acute alcohol intake on the course of acetaminophen overdose. The

Table 1. Univariate analyses of patients with chronic alcohol intake (Chronic alc) vs. patients without chronic alcohol intake (No chronic alc), and patients with acute alcohol intake (Acute alc) vs. patients without acute alcohol intake (No acute alc)

(a) Chronic alc vs. No chronic alc

Variable	Chronic alc ($n = 57$)	No chronic alc ($n = 152$)	P value
Age (years)	39 (17–65)	29 (12–76)	0.0001
Gender (male/female)	28/29	36/116	0.0007
Acetaminophen dose (g)	35 (10–125)	25 (10–150)	0.0042
Acute alcohol intake	21 (36.8%)	24 (15.8%)	0.0021
Hours to antidote (NAC) treatment	22 (1–84)	16 (1–108)	0.13
Death	7 (12.3%)	13 (8.6%)	0.43
Hepatic coma	23 (40.4%)	21 (13.8%)	0.0001
OLTx	2 (3.5%)	0	0.07
Nomogram risk group			
Low	20%	30%	0.48
Intermediate	8%	8%	
High	73%	62%	
Minimum prothrombin index (arbitrary units)	0.18 (0.07–0.95)	0.30 (0.05–0.99)	0.012
Maximum ALT (U/L)	4340 (8–15 150)	2575 (7–24 000)	0.18
Maximum bilirubin (mmol/L)	67 (5–510)	28 (5–345)	0.0002
Minimum platelet count (cells/μL)	76 (3–356)	162 (5–439)	< 0.0001
Maximum creatinine (μmol/L)	145 (62–976)	82 (55–868)	0.0005
pH on admission	7.29 (6.90–7.58)	7.38 (6.80–7.53)	0.25
Acidosis (pH < 7.30) on admission (yes/no)	12/23	10/55	0.042

(b) Acute alc vs. No acute alc

Variable	Acute alc ($n = 45$)	No acute alc ($n = 164$)	P value
Age (years)	37 (15–59)	31 (12–76)	0.12
Gender (male/female)	21/24	42/122	0.010
Acetaminophen dose (g)	37.5 (5–100)	25 (10–150)	0.25
Chronic alcohol intake	21 (46.7%)	36 (22.1%)	0.0012
Hours to antidote (NAC) treatment	12 (1–72)	18 (1–108)	0.053
Death	2 (4.4%)	18 (11.0%)	0.26
Hepatic encephalopathy	9 (20.0%)	34 (20.9%)	1.00
OLTx	2 (4.4%)	0	0.046
Nomogram risk group			
Low	34%	25%	0.49
Intermediate	9%	8%	
High	57%	68%	
Minimum prothrombin index (arbitrary units)	0.37 (0.07–0.95)	0.24 (0.05–1.00)	0.24
Maximum ALT (U/L)	1501 (9–17 850)	4305 (7–24 000)	0.50
Maximum bilirubin (mmol/L)	27 (5–510)	39 (5–498)	0.35
Minimum platelet count (cells/μL)	140 (3–396)	147 (5–439)	1.00
Maximum creatinine (μmol/L)	87 (62–792)	86 (55–976)	0.89
pH on admission	7.39 (7.05–7.58)	7.36 (6.80–7.53)	0.053
Acidosis (pH < 7.30) on admission (yes/no)	3/18	18/61	0.55

Median (range) is indicated. ALT, alanine aminotransferase; NAC, *N*-acetylcysteine; OLTx, orthotopic liver transplantation.

chosen methodology allowed the analysis of the independent influence of both variables, even in patients with both acute and chronic alcohol intake.[27, 28] The study demonstrated that chronic alcohol intake *per se* had a deteriorating influence on the clinical course of acetaminophen overdose, in keeping with most animal studies on this issue.[7, 8, 29] It was clinically important that the relative risk of development of hepatic encephalopathy was more than five-fold increased in patients with chronic alcohol intake compared with non-drinkers, after correction for all other factors including the nomogram risk group distribution. Also, biochemical

Table 2. Logistic regression models, based on initial non-hepatological variables, for the prediction of hepatic encephalopathy and death in acetaminophen overdose

(a) Hepatic encephalopathy model

Variable	Scoring	Regression coefficient	s.e.	*P* value
Chronic alcohol intake	Present: 1 Absent: 0	1.66	0.44	0.0003
Hours to antidote (NAC) treatment	$\log_{10}$(value)	4.32	0.75	< 0.0001
Constant		−7.80	1.18	< 0.0001

NAC, *N*-acetylcysteine.
Model chi-squared = 76.9; d.f. = 2; $P < 0.0001$.

(b) Death model

Variable	Scoring	Regression coefficient	s.e.	*P* value
Chronic alcohol intake*	Present: 1 Absent: 0	0.33	0.53	0.53
Hours to antidote (NAC) treatment	$\log_{10}$(value)	2.57	0.75	0.0008
Constant		−5.88	1.17	< 0.0001

NAC, *N*-acetylcysteine.
Model chi-squared = 16.9; d.f. = 2; $P = 0.0002$.

Table 3. Multiple regression models, based on initial non-hepatological variables, for the prediction of the minimum prothrombin index, maximum alanine aminotransferase (ALT), minimum platelet count, maximum creatinine and maximum bilirubin in acetaminophen overdose

(c) Log_{10}(minimum prothrombin index) model

Variable	Scoring	Regression coefficient	s.e.	*P* value
Chronic alcohol intake	Present: 1 Absent: 0	−0.095	0.038	0.01
Hours to antidote (NAC) treatment	$\log_{10}$(value)	−0.455	0.036	< 0.0001
Acetaminophen dose	$\log_{10}$(g)	−0.192	0.056	0.0007
Age	Years	0.0044	0.0013	0.0009
Constant		−0.100	0.089	0.27

NAC, *N*-acetylcysteine.
Adjusted $R^2 = 0.485$; $P < 0.0001$.

(d) Log_{10}(maximum alanine aminotransferase) model

Variable	Scoring	Regression coefficient	s.e.	*P* value
Chronic alcohol intake	Present: 1 Absent: 0	0.24	0.12	0.05
Hours to antidote (NAC) treatment	$\log_{10}$(value)	1.86	0.12	< 0.0001
Acetaminophen dose	$\log_{10}$(g)	0.72	0.18	0.0001
Age	Years	−0.011	0.004	0.01
Constant		0.034	0.29	0.91

NAC, *N*-acetylcysteine.
Adjusted $R^2 = 0.59$; $P < 0.0001$.

markers of liver dysfunction (prothrombin index, bilirubin, alanine aminotransferase) and related organ dysfunction (creatinine, platelet count) were adversely affected by chronic alcohol intake. Mortality was not significantly affected by chronic alcohol intake; however, we observed a tendency towards increased mortality as the relative risk of death was increased by a factor of 1.4. A study including a greater number of patients will be needed to detect an excess mortality of this magnitude.

Thus, the present study demonstrates a clearly enhanced morbidity in acetaminophen overdose

(e) Minimum platelet count model

Variable	Scoring	Regression coefficient	s.e.	*P* value
Chronic alcohol intake	Present: 1 Absent: 0	−55.8	9.89	< 0.0001
Hours to antidote (NAC) treatment	$\log_{10}$(value)	−91.6	9.2	< 0.0001
Acetaminophen dose	$\log_{10}$(g)	−30.6	14.8	0.04
Constant		313.2	22.7	< 0.0001

NAC, *N*-acetylcysteine.
Adjusted $R^2 = 0.429$; $P < 0.0001$.

(f) Log_{10}(maximum creatinine) model

Variable	Scoring	Regression coefficient	s.e.	*P* value
Chronic alcohol intake	Present: 1 Absent: 0	0.170	0.044	0.0001
Hours to antidote (NAC) treatment	$\log_{10}$(value)	0.300	0.041	< 0.0001
Constant		1.704	0.052	< 0.0001

NAC, *N*-acetylcysteine.
Adjusted $R^2 = 0.252$; $P < 0.0001$.

(g) Log_{10}(maximum bilirubin) model

Variable	Scoring	Regression coefficient	s.e.	*P* value
Chronic alcohol intake	Present: 1 Absent: 0	0.213	0.055	0.0001
Hours to antidote (NAC) treatment	$\log_{10}$(value)	0.689	0.050	< 0.0001
Gender	Females: 1 Males: 0	0.159	0.053	0.003
Constant		0.662	0.063	< 0.0001

NAC, *N*-acetylcysteine.
Adjusted $R^2 = 0.533$; $P < 0.0001$.

Table 4. Adjusted influence of chronic alcohol intake vs. no chronic alcohol intake on variables describing the severity of acetaminophen intoxication. 95% confidence limits are indicated in parentheses

Dependent variable	Influence of chronic alcohol intake	95% confidence interval
(a) Hepatic encephalopathy	Risk increased by a factor of 5.3	(2.2–12.5)
(b) Death	Risk increased by a factor of 1.4	(0.5–3.9)
(c) Minimum prothrombin index	Level decreased by a factor of 0.8	(0.68–0.95)
(d) Maximum alanine aminotransferase	Level increased by a factor of 1.74	(1.01–2.99)
(e) Minimum platelet count	Level decreased by 56×10^9/L	36–75
(f) Maximum creatinine	Level increased by a factor of 1.48	(1.21–1.80)
(g) Maximum bilirubin	Level increased by a factor of 1.63	(1.27–2.09)

patients with chronic alcohol intake, in contrast to suggestions of the opposite.[30] As a clinical consequence, we suggest that patients with chronic alcohol intake and acetaminophen overdose should be even more closely monitored than 'normal patients', and alcoholics should optimally be transferred early to a specialized liver centre.

An important methodological problem in this study is the reliability of the history of alcohol and aceta-

minophen intake in alcoholics. Even though we interviewed the patients and next of kin thoroughly, under-reporting of ethanol (and acetaminophen) intake may have occurred. In more than one-quarter of patients with chronic alcohol intake, a more precise quantitative estimation of ethanol consumption could not be made. The fact that part of the study was retrospective could increase the risk of overlooking details available in a prospective study. At the same time, the addition of retrospectively included patients increased the power of the study. To overcome these problems, the information on alcohol intake was transformed into a simple dichotomous parameter (over/under the 50 g ethanol threshold). As gathering information on alcohol intake is a very important routine of the Liver Unit, we believe that we determined quite precisely whether the threshold was exceeded or not. Furthermore, the definition of acute alcohol intake (≥ 50 g ethanol) may be of influence for the findings. Most animal studies used a 3–6 g ethanol/kg body weight definition,[7, 12, 13] and only a single study used 1 g ethanol/kg body weight.[10] In our patients, the median of 150 g acute ethanol intake approximately corresponds to 2 g/kg body weight. While generalization from rodents to humans may be impossible, the chosen limit corresponds approximately to the animal data. In summary, the above-mentioned possible biases were overcome by the chosen methodology.

The major hepatic pathways of acetaminophen include glucuronidation or sulphation, yielding non-toxic conjugates excreted by the kidney.[31] A second pathway involves the cytochrome P-450 (CYP) system, especially CYP2E1, by which acetaminophen is metabolized to the highly reactive metabolite *N*-acetyl-*p*-benzoquinoneimine, that may bind covalently with hepatic proteins[32] causing cellular necrosis. The toxic effect of *N*-acetyl-*p*-benzoquinoneimine is eliminated by the natural antidote glutathione.[33] Chronic alcoholism could increase acetaminophen toxicity either by short-lived induction of the CYP2E1 pathway[34–36] or by decreasing the hepatic content of glutathione.[8, 37, 38] Studies on healthy adults have reported that *N*-acetyl-*p*-benzoquinoneimine formation is only modestly elevated following a 500-mg acetaminophen dose during ethanol induction,[39] suggesting that factors other than *N*-acetyl-*p*-benzoquinoneimine formation may be responsible for the increased morbidity in patients with chronic alcohol intake. Recent data have also demonstrated that CYP3A is induced by alcohol[40] and may increase acetaminophen hepatotoxicity.[41] Short-term treatment with alcohols of mice without the CYP2E1 gene also enhances acetaminophen toxicity.[42]

Recently, Makin and Williams studied 553 patients with acetaminophen overdose and found no increased susceptibility of hepatotoxicity in drinkers (categorized into light drinkers, moderate drinkers and heavy drinkers) compared with non-drinkers.[20] The development of hepatic encephalopathy and biochemical variables (INR, creatinine), except for the platelet count, were no different between drinkers and non-drinkers. However, the independent influence of chronic alcohol intake was not studied, and so the possibility of confounding between variables cannot be ruled out.

Unexpectedly, acute alcohol intake did not independently influence the course of acetaminophen overdose. This finding is in contrast to observations from animal studies where acute alcohol ingestion marginally decreased the toxic effects of acetaminophen by competitive interaction with CYP2E1.[7, 8, 10, 11, 13, 34] Furthermore, *N*-acetylcysteine antidote treatment, which is paramount in the clinical setting, was not used in these animal studies. It is possible that acute alcohol intake may reduce the protective effects of *N*-acetylcysteine,[43] thus counteracting a possible protective effect on acetaminophen toxicity.

The most important prognostic marker for the severity of the intoxication was the delay from acetaminophen ingestion to the commencement of antidote (*N*-acetylcysteine) treatment, in keeping with previous reports.[21] Because we studied patients with single-dose overdose only, no patients with accidental overdose were included for the analyses. Thereby, the problem of establishing an exact time of the acetaminophen intake was avoided. Hospitalized patients with accidental overdose seem to have more severe hepatotoxicity than suicidal overdose cases and there is a larger proportion of chronic alcoholics.[5, 14] A separate study to evaluate the independent impact of chronic alcohol intake in accidental overdose patients is needed.

In conclusion, chronic alcohol intake independently increased the morbidity in patients with acetaminophen overdose, whereas acute alcohol intake did not affect the clinical course. We suggest that chronic alcohol intake patients with acetaminophen overdose should be very closely monitored, and early transferral to a specialized liver unit should be considered.

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