ORIGINAL INVESTIGATION

Effect of Maximal Daily Doses of Acetaminophen on the Liver of Alcoholic Patients

A Randomized, Double-blind, Placebo-Controlled Trial

Edwin K. Kuffner, MD; Richard C. Dart, MD, PhD; Gregory M. Bogdan, PhD; Robert E. Hill, BSMJ; Edmund Casper, MD; Lisa Darton, MD

Background: Retrospective reports suggest that therapeutic doses of acetaminophen may be associated with fulminant hepatic failure and death in alcoholic patients. Millions of patients use acetaminophen; the prevalence of alcoholism in the United States is 5% to 10%.

Objective: To determine if hepatic injury was associated with maximal therapeutic dosing of acetaminophen to chronic alcohol abuse patients immediately following cessation of alcohol intake (the presumed time of maximal vulnerability).

Methods: Patients entering an alcohol detoxification center were enrolled in a randomized, double-blind, placebo-controlled trial. Exclusion criteria were baseline values of aspartate or alanine aminotransferase greater than 120 U/L, international normalized ratio greater than 1.5, serum acetaminophen level greater than 20 mg/L, or a history of ingesting more than 4 g/d of acetaminophen. Acetaminophen, 1000 mg, or placebo was administered orally 4 times daily for 2 consecutive days and liver test results were monitored for 2 more days. Acetaminophen was not administered until the alcohol had been eliminated.

Results: There were 102 patients in the acetaminophen-treated group and 99 patients in the placebo-treated (control) group. Demographic data, alcohol history, and baseline blood test results were similar in both groups. The mean (SD) aspartate aminotransferase level on day 4 was 38.0±26.7 U/L in the acetaminophen-treated group and 37.5±27.6 U/L in the placebo-treated group. There were 4 patients in the acetaminophen-treated group and 5 in the placebo-treated group who developed an increase in their serum aspartate aminotransferase level to greater than 120 U/L; it did not exceed 200 U/L in any patient. The mean (SD) international normalized ratio on day 4 was 0.96±0.09 in the acetaminophen-treated group and 0.98±0.11 in the placebo-treated group.

Conclusion: Repeated administration of the maximum recommended daily doses of acetaminophen to long-term alcoholic patients was not associated with evidence of liver injury.

Arch Intern Med. 2001;161:2247-2252

From the Rocky Mountain Poison and Drug Center, Denver Health Authority (Drs Kuffner, Dart, and Bogdan and Mr Hill); Department of Psychiatry, Denver Health Medical Center, Denver Health Authority (Drs Casper and Darton); and Department of Surgery, University of Colorado Health Sciences Center (Drs Kuffner and Dart and Mr Hill), Denver.

ACETAMINOPHEN is a safe and effective analgesic and antipyretic when used appropriately. When taken in overdose, particularly large intentional overdose, acetaminophen can cause fulminant hepatic failure and death. In recent years, retrospective case reports and case series have suggested that alcoholic patients may be at risk of acetaminophen-induced hepatic injury and even death following the ingestion of recommended therapeutic doses of acetaminophen.[1] Since the prevalence of alcoholism in the United States is 5% to 10%,[2] a potentially fatal drug-drug interaction could have far-reaching public health consequences.

Acetaminophen and alcohol are metabolized by hepatic cytochrome P450 isoenzymes, particularly CYP2E1.[3,4] The primary metabolites of acetaminophen following a therapeutic dose are nontoxic. However, metabolism produces a small amount of a potentially toxic metabolite, *N*-acetyl-*p*-benzoquinoneimine (NAPQI), which is rapidly detoxified by conjugation with glutathione and excreted in the urine as a mercapturic acid metabolite. When the amount of NAPQI formed overwhelms this detoxification mechanism, however, hepatic injury may develop.[5]

Conditions that increase production of NAPQI or that decrease cellular defenses against NAPQI have been hypothesized to increase the injury associated with a dose of acetaminophen. For example, long-term alcohol use has been shown in animals to induce the activity of CYP2E1, increase the amount of NAPQI produced, and increase the hepatic injury caused by a single, large dose of acetaminophen.[6] Case reports and retrospective case series have described alcoholic patients who developed fulminant hepatic failure in association with

SUBJECTS AND METHODS

STUDY DESIGN AND SUBJECTS

Alcoholic patients were administered placebo or acetaminophen in a randomized, double-blinded, placebo-controlled trial. The study period spanned 4 days: 2 days for acetaminophen administration followed by 2 days of monitoring. The dose of acetaminophen was 1 g, 4 times daily. The study was approved by the institutional review board and included informed consent. Patients received a total of $15 for participation.

Patients 18 years or older entering Denver CARES (Comprehensive Alcohol Receiving and Emergency Services), an alcohol and drug detoxification facility, were eligible for enrollment. Exclusion criteria included a baseline serum aspartate aminotransferase (AST) or alanine aminotransferase (ALT) level greater than 120 U/L, a baseline international normalized ratio (INR) greater than 1.5, a baseline serum acetaminophen level greater than 20 mg/L (therapeutic range, 10-20 mg/L), a positive serum pregnancy test result, a history of ingesting more than 4 g/d of acetaminophen for any of the 4 days preceding enrollment, a history of allergy to acetaminophen, enrollment in any other trial within the preceding 3 months, or clinical alcohol intoxication at the time the first dose of study medication was administered.

A structured medical history was obtained, including specific alcohol, medication, and nutritional components. The alcohol history included the CAGE questionnaire and the Brief Michigan Alcoholism Screening Test (MAST), 2 validated measures of alcoholism.[13,14] The medication history included common drugs that may induce or inhibit the cytochrome P450 microsomal enzyme system. The physical examination included height, weight, and a clinical assessment of nutritional status. The study investigator clinically classified each patient into 1 of the following nutritional categories: normal nutritional status, mild malnutrition, moderate malnutrition, or severe malnutrition.[15] The body mass index (BMI) (the weight, in kilograms, divided by the height, in meters, squared) was calculated.[16]

Laboratory specimens were drawn before the first dose of study medication and in the morning of days 2 and 4 and assayed in the clinical laboratory of Denver Health Medical Center. Baseline laboratory studies included the following: serum acetaminophen level, complete blood cell count, serum electrolyte levels, renal function test results, AST, ALT, and γ-glutamyl transferase (GGT) levels, and INR. Female patients underwent β-human chorionic gonadotropin level testing. On days 2 and 4 of the study, serum electrolyte levels, renal function test results, AST and ALT levels, and INR were determined or evaluated. Alcohol levels were determined at the time of the initial presentation, usually the evening before enrollment, using a breath alcohol analyzer (Intoxilyzer 300; CMI Inc, Owensboro, Ky).

Each patient who met the inclusion criteria was individually randomized using statistical software (StatMate version 1.01I; GraphPad Software Inc, San Diego, Calif). An investigator (G.M.B.) not involved with patient care generated the randomization schedule and maintained the randomization code throughout the trial.

Group assignments were blinded for patients, staff, and investigators. Patients received either acetaminophen purchased commercially (two 500-mg Extra Strength Tylenol tablets; McNeil Consumer Healthcare, Fort Washington, Pa) or 2 placebo tablets in identical pill casings. Study medications were dispensed either by nursing staff or study investigator and recorded on a drug dispensing form. Patients had 24-hour nursing supervision. Patients who left the detoxification facility during the study were dropped from the trial.

Patients received the study drug on days 1 and 2 at 9 AM and at 1, 5, and 9 PM. Phlebotomy was performed between 8 and 9 AM by a study investigator (E.K.K.) on day 2 prior to administration of the study drug and on day 4 prior to discharge from the study.

DATA COLLECTION AND STATISTICAL ANALYSIS

Data were entered into Access 7.0 (Microsoft Corp, Redmond, Wash) and imported into InStat 3.0 (GraphPad Software Inc) for statistical analysis. Categorical variables (sex, race, number of self-reported alcoholic subjects, CAGE answers, number of subjects with a score of 6 or more on the Brief MAST, duration of most recent drinking binge, number of subjects with a detectable blood alcohol level) are presented as frequency of occurrence and were compared by χ^2 test for independence. Continuous variables (age, BMI, baseline values for GGT, AST, ALT, INR, Brief MAST mean score, and mean blood alcohol level) are presented as mean ± SD and comparisons performed using *t* tests to compare excluded subjects (those who failed the screening criteria and those who withdrew before treatment) with those included in the study (both treatment arms), and to compare the 2 treatment groups (acetaminophen-treated vs placebo-treated [control] group). A BMI less than 22 for men and less than 21 for women was used to divide the groups and is suggestive of clinical malnutrition.

A 2-way analysis of variance (ANOVA) was used to assess the significance of changes in liver function test results (ALT level, AST level, and INR, log-transformed) over time following the administration of acetaminophen or placebo, and to test for differences between the acetaminophen-treated and placebo-treated groups. The model was factorial for the treatment group (2 levels: acetaminophen and placebo) and repeated measures for time (3 levels: at baseline, at 2 hours, and at 4 hours after dosing) with interactions. The general linear model calculations were performed using the SPSS statistical package (SPSS, Inc, Chicago, Ill). The Fisher exact test was used to compare the proportion of groups for (1) development of an increase in the level of serum AST or ALT or an INR above baseline; (2) development of an increase in the level of serum AST or ALT above 120 U/L; (3) presence of clinical malnutrition; and (4) use of CYP2E1 inducers and inhibitors.

doses of acetaminophen reportedly within the recommended 4 g/d.[1,7] However, data from human studies are conflicting and the preponderance of data do not indicate that the amount of reactive intermediate produced is increased in the alcoholic patient.[3,8-10]

These retrospective reports have convinced some practitioners to recommend a decreased dose or complete avoidance of acetaminophen in the alcoholic patient.[1] Extensive coverage in the lay press has discouraged patients who drink alcohol from using acetaminophen. If the alcoholic

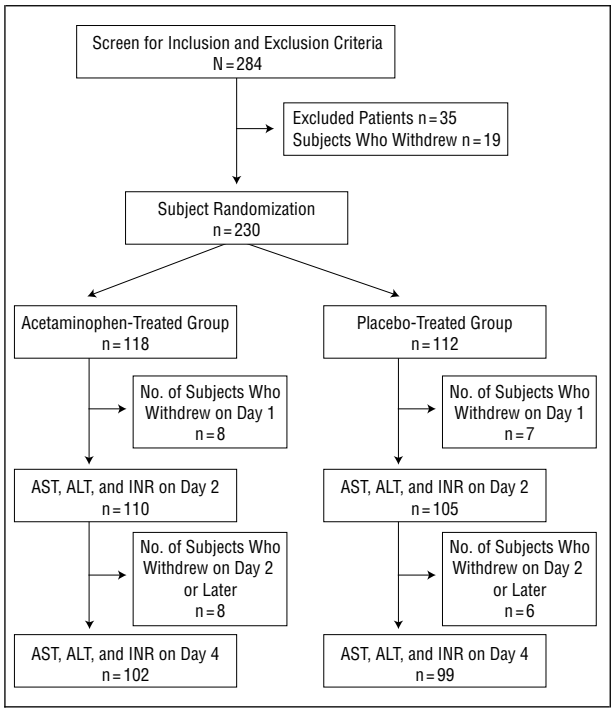
patient is to be advised to avoid acetaminophen, however, the potential adverse effects of this advice must be considered. It seems likely that patients will seek alternative over-the-counter pain medications. Nearly all of these products are nonsteroidal anti-inflammatory agents. Since nonsteroidal medications can produce gastric ulcers and increase the risk of death,[11] their use in alcoholic patients can be dangerous.[12] Because of the serious implications, the magnitude of over-the-counter analgesic and alcohol use and the lack of prospective data, we performed a randomized controlled trial to determine if hepatic injury was associated with maximal therapeutic dosing of acetaminophen to chronic alcohol abuse patients immediately following cessation of alcohol intake (the presumed time of maximal vulnerability). In addition, we assessed the effect of acetaminophen on the subgroups of patients potentially malnourished or exposed to agents that induce the activity of cytochrome P450 enzymes.

RESULTS

There were 284 subjects screened for eligibility: 30 subjects were excluded based on a baseline AST or ALT level greater than 120 U/L, 19 withdrew before randomization, and 5 had previously participated in the trial (**Figure**). The remaining 230 subjects were randomized as follows: 118 to the acetaminophen-treated group and 112 to the placebo-treated group. After randomization, 29 subjects elected not to stay at the facility for the required 4 days. No patient withdrew from the study because of an adverse event. One patient in the study was diagnosed as having a subdural hematoma that was related to head trauma suffered prior to study enrollment. Of the 16 subjects in the acetaminophen-treated group who withdrew, 2 received a single dose, 5 received 2 to 4 doses, and 9 received 5 to 8 doses. Telephone follow-up and medical record review revealed that all subjects who withdrew from the placebo-treated group and 15 of 16 subjects from the acetaminophen-treated group were located and reported no apparent illness following withdrawal from the study. One patient could not be located.

Overall, 201 subjects completed the study: 102 received acetaminophen and 99 received placebo. A comparison of the randomized acetaminophen-treated and placebo-treated groups showed no statistically significant differences (all $P>.05$) in age; sex; race; BMI; baseline levels of GGT, AST, and ALT; and INR values or measures of alcohol use (**Table 1** and **Table 2**). A comparison between subjects who participated in the study and those who failed screening or withdrew before treatment showed that the experimental and excluded groups did not differ significantly for sex, race, BMI, or baseline AST, ALT, and INR values. Excluded subjects were about 3 years younger than included subjects ($P=.01$), had higher GGT values (227 U/L vs 127 U/L, $P<.001$), and had fewer self-reported alcoholic subjects (83% vs 99%, $P<.001$).

Two-way ANOVA showed that there was a significant change in the liver enzyme concentrations over time (for both groups combined), but no significant difference between the groups. The study had a power of 95% to detect a mean difference in the AST level of 13.9 U/L, in the ALT level of 16.6 U/L, and in the INR of 0.05. However, the AST level differed over time in the acetaminophen-treated group, decreased on day 2, and then returned to baseline value. The AST level remained unchanged over time in the placebo-treated group. Four patients in the acetaminophen-treated group and 5 patients in the placebo-treated group developed an AST or ALT level greater than 120 U/L (**Table 3**). No subject in either group developed a serum AST or ALT level above 200 U/L. The highest ALT or AST level was 197 U/L and occurred in the placebo-treated group. The highest INR was 1.75 and also occurred in the placebo-treated group.



Study schematic. AST indicates aspartate aminotransferase level; ALT, alanine aminotransferase level; and INR, international normalized ratio.

A BMI consistent with clinical malnutrition (<22 for men and <21 for women) was found in 34 subjects (33.3 %) in the acetaminophen-treated group and 30 subjects (30.3 %) in the placebo-treated group ($P=.65$). Post hoc subgroup analysis showed no increase in enzyme levels among subjects with a low BMI or those judged malnourished by clinical judgment.

A history of use of CYP2E1-inducing drugs was common: tobacco (78 subjects in each group), phenytoin sodium (4 acetaminophen-treated subjects, 7 placebo-treated subjects), valproate sodium (1 acetaminophen-treated subject, 2 placebo-treated subjects), and phenobarbital sodium (2 placebo-treated subjects). The only subject in the study who reported use of a P450 inhibitor was in the placebo-treated group; the subject was was receiving disulfiram. There was no statistical difference between the 2 groups. Post hoc subgroup analysis showed no increase in either AST or ALT levels in subjects receiving CYP2E1 inducers.

COMMENT

Our study was designed to detect a small change in serum AST and ALT levels, should the administration of

Table 1. Comparison of Baseline Characteristics for Experimental Groups and Excluded or Withdrawn Subjects*

Characteristic	Acetaminophen-Treated Group (n = 102)	Placebo-Treated Group (n = 99)	*P* Value, Acetaminophen- vs Placebo-Treated Group	Excluded or Withdrawn Subjects (n = 83)	*P* Value, Experimental vs Excluded Group
Age, y					
Mean ± SD	43.9 ± 8.6	45.0 ± 8.2	.34	41.6 ± 9.2	.01
Range	27-68	28-70	. . .	23-69	. . .
Men, No. (%)	91 (89)	89 (90)	.99	67 (81)	.07
Race, No. (%) of subjects					
White	50 (49)	52 (53)		51 (61)	
Hispanic	17 (17)	19 (19)		10 (12)	
Black	27 (26)	20 (20)	.6	14 (17)	.3
Other	5 (5)	8 (8)		5 (6)	
Unknown	3 (3)	0 (0)		3 (4)	
Body mass index, kg/m^2					
Mean ± SD	23.6 ± 4.6	23.4 ± 3.5	.59	23.6 ± 2.9	.99
Range	16.6-41.8	16.9-34.0	. . .	18.7-30.3	. . .
γ-Glutamyltransferase level, U/L†					
Mean ± SD	124.6 ± 205.4	128.9 ± 282.1	.34	227.1 ± 304.4	<.001
Range	14-1672	1-1922	. . .	17-1834	. . .
Aspartate aminotransferase level, U/L†					
Mean ± SD	40.0 ± 20.4	41.6 ± 23.5	.77	39.6 ± 18.7‡	.93
Range	14-112	12-116	. . .	15-89	. . .
Alanine aminotransferase level, U/L†					
Mean ± SD	34.6 ± 19.2	36.5 ± 20.2	.48	37.0 ± 23.0‡	.95
Range	9-92	9-109	. . .	9-95	. . .
International normalized ratio†					
Mean ± SD	0.96 ± 0.08	0.98 ± 0.08	.11	0.98 ± 0.09‡	.53
Range	0.80-1.18	0.82-1.34	. . .	0.84-1.35	. . .

*Ellipses indicate does not apply.
†Data normalized for analysis using log transformation.
‡Value includes only patients who enrolled in the trial and later withdrew.

acetaminophen in therapeutic doses to an alcoholic subject produce any degree of hepatotoxic reaction. We found no difference between placebo-treated and alcoholic subjects who received the maximum recommended daily dose of acetaminophen. The study power was 95% to detect a difference in the mean AST level of 14 U/L. Further, subgroup analyses of putative high-risk groups showed no effect on serum AST and ALT levels or on the INR of subjects in our study. Neither the alcoholic subjects with evidence of malnutrition nor those who were treated long-term with agents expected to induce the activity of the cytochrome P450 system showed evidence of increased AST or ALT levels or an INR. A plausible subset of subjects with increased vulnerability to therapeutic doses of acetaminophen has yet to be demonstrated in a study with appropriate experimental design.

Benson[17] administered acetaminophen to patients with chronic liver disease in a prospective study. In a pilot phase, 6 patients with various types of liver cirrhosis were treated with 4 g/d of acetaminophen for 5 days. No change in the AST level was found. Subsequently, 20 patients with liver disease (alcoholic liver disease, Laennec cirrhosis, postnecrotic cirrhosis, chronic active hepatitis, chronic persistent hepatitis, and primary biliary cirrhosis) were randomly assigned to receive either acetaminophen or placebo for 13 days in a crossover trial. There was no difference in the bilirubin, AST, and ALT levels or other studies between the acetaminophen-treated and placebo-treated groups.

In contrast to the evidence from prospective trials, case reports and retrospective case series have described an association of severe hepatic injury and the reported ingestion of therapeutic doses of acetaminophen by alcoholic patients. A systematic review described 25 patients in 20 reports over a 23-year period that described development of hepatic injury in association with the reported use of therapeutic doses of acetaminophen by an alcoholic patient.[18] Only 5 of these case reports contain enough information to credibly implicate acetaminophen. One other case series described a registry of 67 patients in whom hepatic injury developed after ingestion of acetaminophen.[1] The article states that 40% of these patients reported ingestion of therapeutic doses of acetaminophen, but includes data insufficient to assess the relationship to acetaminophen ingestion. The difficulty in interpreting retrospective reports is that they suffer from many methodological weaknesses: incomplete and inaccurate data collection resulting in missing and conflicting data, inaccuracies in the history regarding the dose of acetaminophen ingested, acetaminophen levels that in many cases contradict the reported history of ingestion, and the failure to rule out other causes of hepatotoxic reaction.[18] All reports contained 1 or both of 2 serious flaws: (1) they relied on the patient's history to estimate the dose ingested or (2) other causes of liver injury were not evaluated.

The history is a particularly troublesome challenge in the case of the alcoholic subject. Studies have demonstrated that recent memory is impaired in the alco-

Table 2. Measures of Alcohol Use for Experimental Groups and Excluded or Withdrawn Subjects

Measure of Alcohol Use	Acetaminophen-Treated Group (n = 102)	Placebo-Treated Group (n = 99)	*P* Value, Acetaminophen- vs Placebo-Treated Groups	Excluded or Withdrawn Subjects (n = 83)	*P* Value, Experimental vs Excluded Group
No. (%) of self-reported alcoholic subjects	99 (97)	99 (100)	.25	73 (83)	<.001
CAGE questions,* No. (%) of subjects					
≥2 Yes answers	96 (94)	93 (94)	.99	75 (90)	.31
4 Yes answers	63 (62)	61 (62)		51 (61)	
Brief MAST,† No. (%) of subjects					
Score ≥6 points	100 (98)	98 (99)	.99	77 (93)	.02
Mean score ± SD	23.6 ± 5.6	22.7 ± 5.3	. . .§	22.2 ± 7.8	. . .
Range‡	0-29	0-29	. . .	0-29	. . .
Duration of most recent drinking binge					
<1 wk	24	24	. . .	17	. . .
1-4 wk	34	27	. . .	23	. . .
>1 mo	17	20	. . .	18	. . .
>6 mo	25	24	. . .	17	. . .
Unknown	2	4	. . .	8	. . .
No. (%) of subjects who had a detectable blood alcohol level at presentation	83 (81)	76 (77)	.49	52 (63)	.007
Blood alcohol level at presentation, mg/dL					
Mean ± SD	186.4 ± 109.2	157.0 ± 101.0	0.06	171.7 ± 98.2	.99
Range	0-447	0-370	. . .	0-384	. . .

*CAGE indicates the following: *C* Have you ever felt the need to *c*ut down on your drinking? *A* Have you ever felt *a*nnoyed by criticism of your drinking? *G* Have you ever felt *g*uilty about your drinking? *E* Have you ever taken a drink (*e*ye opener) first thing in the morning? A diagnosis of alcoholism was based on a total of 2 yes answers on the 4 CAGE questions.

†Brief MAST indicates the Brief Michigan Alcohol Screening Test. A diagnosis of alcoholism was based on the score (reference range, 0-29 points).

‡Values indicate the range of the entire Brief MAST score, not the range of the scores for our subjects.

§Ellipses indicate does not apply.

Table 3. Hepatic Aminotransferase Levels After Drug Dosing of Subjects*

Variable	Acetaminophen-Treated Group (n = 102)	Placebo-Treated Group (n = 99)	*P* Value
No. (%) of subjects who developed an AST level above baseline	41 (40.2)	42 (42.4)	.77
No. (%) of subjects who developed an ALT level baseline value (%)	52 (51.0)	62 (62.6)	.12
No. (%) of subjects who developed an INR level above baseline (%)	52 (51.0)	53 (53.5)	.78
No. (%) of subjects who developed an AST or ALT level >120 U/L (%)	4 (3.9)	5 (5.1)	.75
No. (%) of subjects who developed an AST or ALT level >1000 U/L or an INR >1.5	0 (0)	1 (1.0)	.49
Day 2			
AST level, mean ± SD, U/L	33.3 ± 21.4	38.0 ± 24.7	. . .
ALT level, mean ± SD, U/L	33.1 ± 22.0	37.3 ± 23.9	. . .
INR, mean ± SD	0.95 ± 0.07	0.95 ± 0.11	. . .
Day 4			
AST level, mean ± SD, U/L	38.0 ± 26.7	37.5 ± 27.6	. . .
ALT level, mean ± SD, U/L	40.1 ± 30.9	41.9 ± 33.9	. . .
INR, mean ± SD	0.96 ± 0.09	0.98 ± 0.11	. . .

Test	Group Difference	Time-Dependence	Interaction
AST	*P* = .64	*P* < .001	*P* = .06
ALT	*P* = .34	*P* < .001	*P* = .23
INR	*P* = .76	*P* = .07	*P* = .19

*AST indicates aspartate aminotransferase; ALT, alanine aminotransferase; INR, international normalized ratio; and ellipses, does not apply.

holic subject.[19] For example, nearly all of the reports of hepatic injury associated with therapeutic use of acetaminophen include obviously conflicting data such as serum acetaminophen levels inconsistent with therapeutic doses of acetaminophen, hepatic histologic abnormalities inconsistent with acetaminophen toxic reactions, suicidal gestures that presumably involved a therapeutic dose, and other contradictions. Because of their retrospective design and the frequently conflicting data, causation cannot be ascertained from the data available.

Our study avoided the weakness of retrospective reports. We administered a known dose of acetaminophen, beginning at the time of maximal CYP2E1 induc-

tion. Although we did not measure CYP2E1 activity in our subjects directly, the population had a very high incidence of alcoholism as assessed by 2 valid standard alcoholism screening tools. Further, nearly all of our subjects were intoxicated at the time of enrollment. Since studies have shown that acute and concurrent alcohol intoxication may actually protect against acetaminophen-induced hepatotoxic reactions,[6,20] we initiated administration of study medications soon after the subject achieved sobriety, thereby assuring that they were at maximal vulnerability for developing a toxic reaction. If subjects did not develop hepatic damage when they were not intoxicated with alcohol, it is unlikely that they would have developed a hepatotoxic reaction when they were intoxicated and protected against acetaminophen-induced hepatotoxic reaction. Also if subjects did not develop hepatic damage when their CYP2E1 was maximally induced, it is unlikely that they would have developed a hepatotoxic reaction as their CYP2E1 induction waned.[21] Our subjects were at maximal vulnerability for developing a toxic reaction.

Substantial variations in the AST and ALT levels were observed in our subjects at all periods throughout our study (Table 3). These fluctuations emphasize the importance of a randomized placebo-controlled trial in the evaluation of a hepatotoxic reaction in alcoholic subjects. If we had administered acetaminophen to all subjects, instead of including a placebo comparison group, these data would have indicated that 83 subjects (41%) experienced a rise in their serum AST level and that 1 subject's level reached 197 U/L. Further, an INR as high as 1.75 could theoretically have been attributed to acetaminophen treatment. The inclusion of a placebo group allowed us to demonstrate that fluctuations in the AST and ALT levels should be expected in the alcoholic subject population.

Limitations of our study include that the acetaminophen dose did not exceed the maximum therapeutic daily dose of acetaminophen and was administered for only 2 days. Therefore, our data should not be applied to supratherapeutic or overdose ingestions of acetaminophen. Our study also excluded subjects who had AST or ALT elevations greater than 120 U/L. Although unlikely based on human CYP2E1-induction data,[21] it is possible that administration of acetaminophen for a longer period than 2 days is required for alcoholic patients to manifest a hepatotoxic reaction. It is also possible that a hepatotoxic reaction from therapeutic dosing of acetaminophen is an idiosyncratic and rare event that would only be detected in a study with an extremely large sample size.

Despite the weakness of retrospective data, some authors[1] have asserted that alcoholic patients should use reduced doses of acetaminophen or avoid it entirely. This recommendation creates a therapeutic dilemma: the common alternatives to acetaminophen are aspirin and other nonsteroidal anti-inflammatory agents. Unfortunately, these drugs have been shown to cause life-threatening gastrointestinal bleeding in both normal subjects and alcoholic subjects.[11,12] Recommendations to lower the acetaminophen dose in alcoholic subjects are based on retrospective information. Since this study and other prospective studies have failed to find evidence of liver injury in humans,[17,18] even in purportedly high-risk groups, we believe that such a recommendation is unwarranted.

Accepted for publication March 29, 2001.

This research was supported by a grant from McNeil Consumer Healthcare, Fort Washington, Pa.

Presented at the North American Congress of Clinical Toxicology, San Diego, Calif, October 2, 1999.

We thank the counseling, nursing, and support staff at Denver CARES and the laboratory staff at the Denver Health Medical Center for their help in conducting this trial.

Corresponding author: Edwin K. Kuffner, MD, Rocky Mountain Poison and Drug Center, 1010 Yosemite Cir, Denver, CO 80230 (e-mail: EKuffner@rmpdc.org).

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