Acetaminophen Use in Patients Who Drink Alcohol: Current Study Evidence

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Abstract

Package labeling for all over-the-counter pain relievers and fever reducers warns patients who drink 3 or more alcoholic beverages daily to consult with a physician before using these products. In the absence of accurate, consistent data, physicians have relied on retrospective and anecdotal evidence, which has perhaps led to greater restrictions on acetaminophen use than necessary for patients who consume alcohol. Recently, a well-controlled clinical study was conducted to more rigorously characterize the risk to alcohol users taking acetaminophen. In this randomized, double-blind, placebo-controlled trial, patients enrolled in a drug detoxification facility received 1000 mg acetaminophen or placebo 4 times daily for 2 consecutive days immediately after discontinuing alcohol use. Serum aspartate aminotransferase and alanine aminotransferase levels, used to detect hepatic necrosis or liver disease, were monitored at baseline and again both during and after the study. Results for 201 patients completing the study showed no statistically significant difference in liver function tests for 102 patients receiving acetaminophen compared with 99 patients receiving placebo. Researchers concluded that there was no increase in liver toxicity among alcoholic patients given the maximal therapeutic dose (4 g/day) of acetaminophen and no clinical evidence of increased risk for these patients when acetaminophen is used within recommended doses.

In 1998, the Food and Drug Administration announced that all over-the-counter (OTC) pain relievers and fever reducers must carry a warning as part of the package labeling directing people who consume 3 or more alcoholic drinks daily to consult with a physician before using those products. The precautions were included to inform users of these medications that chronic alcohol consumption may increase the risk of both liver damage associated with the use of acetaminophen and stomach bleeding associated with the use of aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs).[1]

The impetus for requiring an alcohol warning on OTC analgesics containing acetaminophen was prompted by case reports that claimed alcoholic patients develop hepatic injury when using acetaminophen. There are metabolic concerns that lend credence to these claims. First, even in the absence of chronic alcohol use, untreated acute acetaminophen overdose is sometimes associated with hepatic necrosis and fulminant liver failure.[2] Following an acute acetaminophen overdose, increased amounts of the potentially toxic metabolite N-acetyl-p-benzoquinone imine (NAPQI) can accumulate, reducing hepatic levels of glutathione, which detoxifies NAPQI. Secondly, the hepatic cytochrome P450 enzyme, specifically CYP2E1, is responsible for metabolizing acetaminophen to the toxic metabolite, NAPQI.[3] In addition, chronic alcohol use is associated with induction of CYP2E1. Human studies are conflicting as to whether chronic alcohol use can really increase the

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amount of NAPQI formed following a therapeutic dose of acetaminophen and it is unknown if chronic alcohol users are at increased risk following an acute overdose of acetaminophen.[4-7]

Although the dangers of acute acetaminophen overdose and the potential for an alcohol-acetaminophen drug-drug interaction following therapeutic doses of acetaminophen in alcoholic patients have been well publicized, many physicians, pharmacists, and healthcare facilities do not have clear treatment guidelines about the appropriate therapeutic use of acetaminophen in patients who consume alcohol. Package labeling instructs patients who consume alcohol to consult with a physician before using acetaminophen, but clinical recommendations vary significantly. Treatment guidelines vary significantly and are often based on information that does not meet the "gold standard" of a randomized, double-blind, placebo-controlled trial.[8]

Retrospective patient data and theoretical metabolic concerns have led some clinicians to recommend reduced therapeutic dosages of acetaminophen for alcoholic patients, or even to recommend against its use entirely.[9] There are currently no data from well-controlled clinical trials in people to suggest that the maximal recommended therapeutic dose of acetaminophen, less than or equal to 4 g/day, needs to be reduced for patients who consume alcohol.[8] Physicians who recommend against any use of acetaminophen by alcoholic patients need to consider the ramifications of this recommendation. Alcoholic patients who use other OTC analgesics such as aspirin or NSAIDs are at risk for gastrointestinal hemorrhage and renal complications. Although the relative risk of acetaminophen and NSAID use by alcoholic patients has not been addressed in a well-designed study, based upon the available data it is likely that there is a much greater risk of morbidity and mortality associated with NSAID use.[10,11]

To address the need for a more scientifically rigorous determination of the risk of acetaminophen use among alcoholic patients, a study was conducted among patients enrolled in an alcohol detoxification program. The objective of this randomized, double-blind, placebo-controlled study was to determine whether alcoholic patients are at increased risk for hepatic injury after ingestion of the maximal therapeutic dose of acetaminophen.

··· METHODS ···

The study population was drawn from patients 18 years or older enrolled in a drug detoxification facility. A total of 230 patients were randomized to 2 groups to receive either 1000 mg acetaminophen or placebo 4 times daily for 2 consecutive days. Liver function was monitored for an additional 2 days. Study medication was not administered until patients were clinically sober. Patients were excluded from the study if their baseline serum aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels were greater than 120 U/L. Other exclusion criteria included the following: baseline international normalized ratio (INR) greater than 1.5;

Table 1. Baseline Demographic Characteristics

Characteristics	Acetaminophen Group (n = 102)	Placebo Group (n = 99)
Mean age (years) ± SD	43.9 ± 8.6	45.0 ± 8.2
Men	91 (89%)	89 (90%)
Race		
White	50 (49%)	52 (53%)
Hispanic	17 (17%)	19 (19%)
Black	27 (26%)	20 (20%)
Other	5 (5%)	8 (8%)
Unknown	3 (3%)	0 (0%)
Mean body mass index (kg/m^2) ± SD	23.6 ± 4.6	23.4 ± 3.5

SD = standard deviation.
Source: Kuffner EK, Dart RC, Bogdan GM, et al. Effect of maximal daily doses of acetaminophen on the liver of alcoholic patients. A randomized, double-blind, placebo-controlled trial. *Arch Intern Med* 2001;161:2247-2252. Adapted with permission.

serum acetaminophen level greater than 20 mg/L; ingestion of more than 4000 mg/day acetaminophen for 4 days prior to study enrollment; positive pregnancy test; acetaminophen allergy; enrollment in another trial during the prior 3 months; or alcohol intoxication at the time designated for initial administration of study medication. A total of 29 people chose to withdraw after randomization; none of the withdrawals was related to adverse events. A total of 201 patients completed the study: 102 in the acetaminophen group and 99 in the placebo group. There were no statistically significant differences in demographic or clinical characteristics between the 2 groups. **Table 1** summarizes baseline characteristics of the study participants.[12]

Laboratory tests were conducted at baseline and on days 2 and 4 of the study. Baseline tests measured serum levels of acetaminophen, serum electrolyte levels, renal function, AST and ALT levels, and INR, along with other standard values such as blood cell count. Midstudy and poststudy tests measured serum electrolyte levels, renal function, AST and ALT levels, and INR.

A 2-way analysis of variance (ANOVA) test was used to calculate changes in liver function based on ALT and AST levels, as well as to calculate INR over time following the administration of study medication. ANOVA was also used to assess clinical differences between the active treatment and placebo groups. The Fisher's exact test was used to compare the 2 groups for increased AST or ALT levels or INR above baseline, AST or ALT levels above 120 U/L, nutritional status, and the presence of other agents that might induce or inhibit the CYP2E1 enzyme.

··· RESULTS ···

Study variables included AST, ALT, and INR measurements above baseline; AST or ALT levels exceeding 120 U/L; and AST or ALT levels exceeding 1000 U/L or INR greater than 1.5. **Table 2** summarizes mean values at baseline and at days 2 and 4 for each group.[12] There were no statistically significant differences between the treatment and placebo groups for each variable. Among acetaminophen-treated patients, higher-than-baseline AST levels developed in 40.2%, and higher-than-baseline ALT levels developed in 51%. In comparison, among patients taking placebo, higher-than-baseline AST levels developed in 42.4%, and higher-than-baseline ALT levels developed in 62.6%. Four patients in the acetaminophen group and 5 patients in the placebo group had AST or ALT levels exceeding 120 U/L (P = .75). The highest INR reached was 1.75, which occurred in 1 patient in the placebo group. None of the patients in the acetaminophen group had an INR above 1.5. In other analyses, malnutrition, which was found in 34 patients in the acetaminophen group and in 30 patients in the placebo

Table 2. Mean Hepatic Enzyme Levels (±SD)

Variable	Acetaminophen Group (n = 102)	Placebo Group (n = 99)
Baseline		
AST	40.0 ± 20.4	41.6 ± 23.5
ALT	34.6 ± 19.2	36.5 ± 20.2
INR	0.96 ± 0.08	0.98 ± 0.08
Day 2		
AST	33.3 ± 21.4	38.0 ± 24.7
ALT	33.1 ± 22.0	37.3 ± 23.9
INR	0.95 ± 0.07	0.95 ± 0.11
Day 4		
AST	38.0 ± 26.7	37.5 ± 27.6
ALT	40.1 ± 30.9	41.9 ± 33.9
INR	0.96 ± 0.09	0.98 ± 0.11

AST = aspartate aminotransferase; ALT = alanine aminotransferase; INR = international normalized ratio; SD = standard deviation.
Source: Reference 12.

group, did not affect liver enzyme levels. The presence of other agents that induce the CYP2E1 metabolic pathway also did not affect liver enzyme levels in either the active treatment or placebo group.

This study found no increase in liver enzyme levels that would suggest increased liver toxicity among alcoholic patients who receive the maximal therapeutic dose (4 g/day) of acetaminophen.

··· DISCUSSION ···

This study was designed to meet rigorous clinical standards to clearly assess the risk of therapeutic acetaminophen use for chronic alcohol users. Currently, physicians and pharmacists who must advise patients who use alcohol about the appropriate use of acetaminophen or other OTC pain relievers do not have adequate guidance that is based on well-designed, prospective trials. Information available to clinicians is often contradictory and may recommend against the use of acetaminophen at all in these patients, without providing another treatment option with fewer risks. Based on the study results presented here, however, there is no clinical evidence of increased risk for alcoholic patients using acetaminophen within recommended doses.

Certain clarifications are necessary. This study was not designed to evaluate the risk of acetaminophen doses beyond the maximum recommended dose. Clinicians should continue to advise all patients, whether or not they consume alcohol, that they must never exceed the maximum recommended dose of acetaminophen, 4 g/day. In addition, although this study found no effect on patients who also receive other drugs that induce CYP2E1, it is important to recognize the recent concern about drug-drug interactions that result from the inhibition or induction of hepatic metabolic pathways. This includes the isoenzyme P450 system, which includes CYP2E1. Physicians and pharmacists should continue to emphasize to patients the necessity of disclosing all medications they are taking so that the potential for adverse events can be decreased. One obvious question is, how might the results of this study have been different if patients had measurable systemic alcohol levels while ingesting acetaminophen? In fact, the presence of ethanol has been shown in animal studies to provide some protective effects against liver damage by inhibiting biotransformation of acetaminophen to its metabolites.[13,14] Therefore, chronic alcohol use contributes to liver damage and impaired metabolism, but while present in the system, it slows the production of toxic metabolites produced by acetaminophen. Presumably, alcoholic patients who no longer have alcohol in their systems may be at highest risk for liver damage. The study presented here includes patients who were given initial study medication soon after becoming sober, when enzyme induction is near its highest levels.

A thorough literature review related to the use of acetaminophen in alcoholic patients reveals that the most stringently controlled studies (ie, randomized, controlled trials and prospective, nonrandomized trials) have not demonstrated evidence of greater risk for alcoholic patients when they use recommended doses of acetaminophen. In contrast, the association of liver injury and a history of acetaminophen use is found only in retrospective case studies. Because of inconsistencies in the history obtained from an alcoholic patient, variation in dosage regimens used, and other methodologic variability of case reports, no reliable conclusions can be drawn from these data.[8]

Additional study of the appropriate use of acetaminophen in alcoholic patients is needed to provide physicians, nurses, and pharmacists with enough data to develop specific treatment recommendations. Current clinical evidence does not support a need to reduce the dose of acetaminophen given to patients who use alcohol, nor does the evidence support prohibiting the use of acetaminophen entirely in these patients.

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