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Use of Over-the-Counter Analgesics Is Not Associated With Acute Decompensation in Patients With Cirrhosis

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Abstract

BACKGROUND & AIMS—Over-the-counter analgesics have been proposed to lead to decompensation of compensated cirrhosis or to further decompensation of an already decompensated patient. We performed a prospective, case-control study to investigate the effects of analgesics on acute hepatic decompensation.

METHODS—Data from consecutive cirrhotic patients hospitalized at 2 tertiary care hospitals for decompensation of cirrhosis (cases, n = 91) were compared with that from consecutive patients with compensated cirrhosis that were followed in the liver clinic (n = 153) and with randomly selected noncirrhotic patients concurrently hospitalized with the cases (n = 89). All patients were given a structured questionnaire to collect information on recent use of acetaminophen, nonsteroidal anti-inflammatory drugs and alcohol.

RESULTS—Only 32 (35%) of the cirrhotic patients used over-the-counter analgesics (19% acetaminophen, 16% nonsteroidal anti-inflammatory drugs), compared with 80 of the cirrhotic controls (52%; 25% acetaminophen, 31% nonsteroidal anti-inflammatory drugs), and 62 (70%) of the noncirrhotic controls. Acetaminophen use did not differ between groups, even for those with recent alcohol use. The doses and days of nonsteroidal anti-inflammatory drug use were higher among cirrhotic patients, compared with controls. Alcohol ingestion was significantly greater among patients with alcoholic cirrhosis, compared with controls.

CONCLUSIONS—In patients with cirrhosis, acetaminophen use at doses lower than those recommended is not associated with acute hepatic decompensation, even in patients with recent alcohol ingestion. Nonsteroidal anti-inflammatory drugs might be associated with deleterious effects on cirrhosis. Alcohol ingestion is associated with decompensation in patients with alcoholic cirrhosis.

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Conflicts of interest

The authors disclose no conflicts.

This article has an accompanying continuing medical education activity on page 914. Learning Objectives—At the end of this activity the learner should identify the role of acetaminophen use and use of nonsteroidal drugs in promoting decompensation of liver disease in patients with cirrhosis.

Over-the-counter analgesics (OTCAs), specifically acetaminophen and nonsteroidal anti-inflammatory drugs (including aspirin, ibuprofen, naproxen, sulindac), can theoretically lead to decompensation in a patient with compensated cirrhosis or to further decompensation in an already decompensated patient (“acute-on-chronic” liver failure), however, this has not been prospectively evaluated. Acetaminophen (APAP, *N*-acetyl-para-aminophenol) is an intrinsic hepatotoxin that produces dose-related hepatocellular necrosis, particularly in the setting of chronic alcohol consumption in which therapeutic doses of APAP are sufficient to produce acute hepatitis.¹ Recent studies have demonstrated that unintentional APAP intoxication over a long period rather than intentional massive ingestion is the most common cause of acute liver failure in the United States.^{2,3} On the other hand, nonsteroidal anti-inflammatory drugs (NSAIDs), in addition to having a potential for idiosyncratic liver injury, blunt the response to diuretics in patients with cirrhosis and ascites and can also promote renal vasoconstriction thereby producing acute kidney injury.

To our knowledge, the role of OTCAs (APAP and NSAIDs) in precipitating acute decompensation of cirrhosis has not been investigated prospectively and was the objective of this study.

Methods

Study Design

The study was designed as a case-control study in which consecutive unique patients with cirrhosis hospitalized for “acute hepatic decompensation” (cirrhotic cases) between August 2000 and May 2002 were compared with consecutive patients with cirrhosis who had not been hospitalized in the previous 3 months and in the month following enrollment (cirrhotic controls) and with patients without cirrhosis hospitalized at the same time as the cases (noncirrhotic controls). Cases were identified through daily surveillance on the wards and intensive care units. Cirrhotic controls were enrolled from the liver clinics. The second control group of noncirrhotic patients was selected randomly by enrolling 1 patient in the room adjacent to each case patient’s room. This group had the purpose of excluding the possibility that patients would recall recent medication and/or alcohol use more specifically and completely than controls, due to the fact that they linked their hospitalization event to this exposure (recall bias). Each patient was only included once in the study.

The diagnosis of cirrhosis was established by clinical, biochemical, ultrasonographic, and/or histological criteria. Acute hepatic decompensation was defined as the development of any of the following: variceal hemorrhage, new or worsening ascites, encephalopathy, jaundice, spontaneous bacterial peritonitis, spontaneous bacteremia, and/or renal dysfunction.

Data Collection

Data were collected using a specially designed questionnaire administered by a research associate not directly involved in the study. This interview included demographic characteristics (age, gender, race), prescription medications, and information regarding OTCAs, including quantity, frequency, and type of preparation(s). Specifically, patients were asked about any OTCA they may have used in the past 30 days and for each OTCA, a 30-day calendar was used to assess the amount of OTCA used on each day in those 30 days. The total dose was based on the sum of the dose for each OTCA in the 30-day period. Because even moderate alcohol intake may facilitate APAP hepatotoxicity,¹ data on alcohol consumption were obtained using the 30-day timeline follow-back; that is, alcohol consumption over the month prior to hospitalization. In addition, the Skinner Lifetime Drinking History Questionnaire was used to ascertain the patient’s lifetime alcohol consumption.⁴ To calculate the grams of alcohol consumed, each drink of alcohol was

considered equivalent to 10 grams (alcohol content of a standard drink in the United States). The interview of patients who were admitted for encephalopathy was delayed until the encephalopathy had clinically resolved. Additional information regarding other medications (type and dose), illicit drug use, etiology of cirrhosis, presence and type of past decompensating events, and parameters of liver function (bilirubin, albumin, prothrombin time, international normalized ratio [INR] [ratio of patient's prothrombin time to control prothrombin time], Child–Turcotte–Pugh [CTP] score and class) were obtained at time of enrollment. Model for End-Stage Liver Disease (MELD) was calculated for cases using bilirubin, INR, and creatinine values.⁵ In order to ensure that there was no education bias (ie, that less sick controls would have been less informed about potential dangers of OTCA than patients), information on prior counseling regarding OTCA use was also collected.

The primary outcome was an assessment of OTCA (APAP and NSAID) use between patients and control subjects to see if it played any role in decompensation of cirrhosis. The secondary outcomes included assessment of alcohol use among the 3 groups. We also performed a subanalysis in the subgroup of cases and controls that could be matched by age (± 5 years in the case of noncirrhotic controls) and CTP class.

Statistical Methods

In order to detect a 50% exposure rate of difference for OTCA between cases and controls (50% exposure rate in cirrhotic controls, 75% in cirrhotic cases), with a 90% power, 85 patients in each group would be necessary for a total of 170 patients with cirrhosis plus 85 noncirrhotic controls. Data are expressed as median with ranges. Fisher's exact test was used to compare categorical variables. The Mann–Whitney and the Kruskal–Wallis tests were used to compare quantitative variables. The statistical software package SPSS for Windows (SPSS Inc, version 11.5, Chicago, IL) was used to analyze the data, and $P < .05$ was considered a significant difference.

Results

Patient Characteristics

In the period between August 2000 and May 2002 (end of the study), 333 patients were enrolled: 91 cirrhotic cases, 153 cirrhotic controls, and 89 noncirrhotic controls. Forty-five cases could be matched by age and CTP class to 45 cirrhotic controls.

Table 1 shows the demographic characteristics of patients included in the study. Among cirrhotic cases, alcohol was the most common etiology, while among cirrhotic controls viral hepatitis (hepatitis C or B) was the most common etiology. Liver disease was more severe in cases than in controls as reflected by significantly lower mean arterial pressure, albumin, and significantly higher serum bilirubin, INR, and CTP score (Table 1). Median MELD score in cirrhotic cases at the time of admission was 19 (range 9–49). Median creatinine at admission in cirrhotic cases was 1 mg/dL (range 0.5–8.1), while median aspartate aminotransferase (AST) at admission was 77 IU/dL (range 11–325). Twenty-six cases (29%) were counseled regarding the use of OTCAs compared with 74/153 (48%) cirrhotic controls ($P = .004$). None of the patients was taking sedatives or any other prescription medications that could have led to decompensation of cirrhosis.

Causes for Admission

Table 2 illustrates the specific decompensating event leading to admission in all cirrhotic cases and in the 45 cirrhotic cases that could be subsequently matched by age and CTP class to cirrhotic controls (see below). No significant differences were observed between both

groups although hepatic encephalopathy was the most common cause for hospitalization in the former group and variceal hemorrhage was more common in the latter group.

OTCA Use

As shown in Table 3, a lower proportion of cirrhotic cases used OTCA compared with either of the control groups with highest use observed in noncirrhotic controls. The same pattern was observed independent of the type of OTCA (APAP or NSAIDs) used. Among patients who used APAP, the dose and amount used in the previous 30 days did not differ among the 3 study groups (Table 3). In cirrhotic cases, the highest dose of APAP used in a single day was 1500 mg (for 2 consecutive days) by 1 patient. The decompensation leading to admission in this patient was encephalopathy; AST at admission was 38 IU/L and peaked at 99 IU/L and creatinine at admission was 0.9 mg/dL with a peak of 1.1 mg/dL. This patient did not use any alcohol in the past 30 days. The highest dose of APAP used by a cirrhotic case in a 30-day period was 39 grams (1300 mg per day for each of the 30 days). The decompensation leading to admission in this patient was new ascites; AST at admission was 115 IU/L and peaked at 117 IU/L, while creatinine was 1 mg/dL at admission and peaked at 1.1 mg/dL. This patient used 56 grams of alcohol for 1 day in the previous 30 days (2 days prior to admission). The highest dose of APAP used by a cirrhotic control patient in a single day was 3 grams during 2 consecutive days. This patient did not use any alcohol in the past 30 days. The highest dose of APAP used by a cirrhotic control patient in a 30-day period was 24.4 grams (975 mg/day for 25 days). This patient used 42 grams of alcohol in the previous month.

The most frequently used NSAIDs were ibuprofen, aspirin, and naproxen. Although the rate of use was not different among the 3 groups and although the number of cirrhotic cases that used NSAIDs was small (15/91 or 16%), they used them for more days and the dose used was larger than in cirrhotic control subjects (Table 3). Of 15 cirrhotic patients who used NSAIDs, 7 (47%) had worsening ascites at admission, compared with 20/76 (26%) of patients who had not used NSAIDs ($P = .13$).

Alcohol Use

As shown in Table 4, there was no difference in the proportion of patients using alcohol in the 3 groups in the 30 days preceding enrollment. However, cirrhotic patients ingested a significantly greater amount of alcohol and for more days than both control groups during this time period. Significantly greater alcohol consumption in cirrhotic patients (compared with cirrhotic control subjects) applied to those with an alcoholic etiology but not to those with a nonalcoholic etiology (Table 5). APAP use was not significantly different between subjects with alcoholic and nonalcoholic etiologies (Table 5). APAP use in patients who had ingested alcohol in the prior 30 days was not different among the 3 groups. Of 25 cirrhotic subjects who used alcohol in the prior 30 days, 4 (16%) used APAP, compared with 9/30 (30%) cirrhotic control subjects and 11/29 (38%) noncirrhotic control subjects ($P = .20$).

Matched Cases and Controls

As mentioned previously, 45 patients could be matched with 1 cirrhotic control subject (matched by age and CTP score) and with 1 noncirrhotic control subject (matched by age). Analysis of this subgroup of patients yielded the same results obtained with the whole group (Table 6).

Discussion

Decompensated cirrhosis is defined by the development of ascites, variceal hemorrhage, encephalopathy, or jaundice. It is at this stage of cirrhosis that the patient is at risk of dying

from liver disease.⁶ Patients with cirrhosis are usually hospitalized when the first episode of decompensation occurs or when an already decompensated patient deteriorates further. A superimposed acute injury (acute-on-chronic event) can precipitate decompensation in the compensated patient or lead to further deterioration in the decompensated patient. A typical example of an acute-on-chronic event is the development of alcoholic hepatitis in a patient with cirrhosis. Drug-induced hepatotoxicity can also potentially induce acute-on-chronic injury and drugs that would be most concerning are the commonly used OTCAs, APAP-containing compounds, and NSAIDs.

APAP-induced hepatotoxicity is the main cause of acute liver failure in the United States.² APAP causes liver damage in a dose-related fashion; with severe hepatotoxicity resulting from single acute ingestion of over 15 grams.⁷ However, recent studies have demonstrated that chronic therapeutic use rather than acute massive ingestion of APAP is a more common cause of acute liver failure in the United States.^{2,3} Furthermore, the at-risk dose may be lower in the presence of chronic alcohol use or malnutrition, both of which may be present in patients with cirrhosis. In these patients therapeutic doses (4 g/day) can produce liver injury.^{1,7,8} Although reduced drug metabolism in patients with cirrhosis does not seem to have a significant impact on the frequency of hepatotoxicity, it is conceivable that patients with alcoholic cirrhosis who are actively drinking would be more susceptible to develop acute-on-chronic liver injury from lower doses of APAP.⁹ On the other hand, NSAIDs can produce idiosyncratic acute hepatocellular necrosis or cholestatic damage,^{10,11} and their use in cirrhosis could potentially also lead to an acute-on-chronic liver injury. More importantly, by inhibiting prostaglandin synthesis, NSAIDs impair their protective renal vasodilating effect and have been shown to blunt the natriuretic effect of diuretics,^{12,13} reduce sodium and water excretion, creatinine clearance, and glomerular filtration rate,^{12,14-22} not only in patients with decompensated cirrhosis but also in those with compensated disease.²³ Additionally, in a case-control study NSAIDs were associated with the development of first variceal hemorrhage.²⁴ It is therefore conceivable that OTCAs could be an important contributor of acute hepatic decompensation in cirrhosis.

Our prospective study was based on determining OTCA use in a 30-day period prior to the admission of patients with cirrhosis who had an acute decompensation of cirrhosis and comparing it with OTCA use in patients with stable cirrhosis followed in the outpatient clinic. The working hypothesis was that a higher proportion of patients with acute decompensation would have used some form of OTCA in the preceding month. However, our results actually show that a lower proportion of patients with cirrhosis use OTCAs in general (compared with concurrently hospitalized noncirrhotic patients), and that an even lower proportion of patients admitted with acute decompensation had used them in the preceding month, suggesting that OTCAs do not contribute to acute hepatic decompensation in cirrhosis. This is clear for APAP that was used by only one fifth of the cirrhotic patients at daily doses that were equivalent to those used by cirrhotic control subjects, and that never exceeded the therapeutic dose of 4 g/day. Additionally, APAP use in patients with active alcohol use was not different between patients and control subjects. The case for NSAIDs is not as clear. Although there were no differences in the proportion of patients and control subjects that used NSAIDs, cirrhotic patients used larger doses and for more days than control subjects, indicating that NSAIDs may have contributed to acute decompensation in these patients. In fact, although not statistically significant because of the small numbers of patients who used NSAIDs, about half the patients that had used NSAIDs prior to admission were admitted with worsening ascites compared with 25% of patients who had not used them.

Not unexpectedly, 1 of the strongest results of the study and 1 that validates our study design refers to alcohol use. In patients with an alcoholic etiology of cirrhosis, the amount of

alcohol ingested in the preceding 30 days was significantly higher in patients than in control subjects, supporting the important role that continued alcohol ingestion plays in the acute decompensation of patients with alcoholic cirrhosis.

There are some limitations to our study including relying on patients' recall, not collecting information on herbal supplements that could have contributed to decompensation, and the relatively small number of patients that took APAP and NSAIDs. We included a control group of hospitalized patients without cirrhosis to ensure that recall of cirrhotic cases would not be greater than that of cirrhotic control subjects but we actually found that the highest rate of OTCA use occurred among noncirrhotic control subjects, and the lowest was among cirrhotic patients. Although the interview of cirrhotic patients admitted with encephalopathy was delayed until its resolution, it is possible that these patients could have remained with a certain degree of encephalopathy and a potentially greater recall impairment. Nevertheless, as mentioned above, the results on alcohol ingestion indicate that recall was not a problem among patients. Furthermore, OTCA use between patients admitted with encephalopathy (12/36, 32%) and those admitted for other causes (20/54, 37%) was not different ($P = .65$) (data not shown).

In conclusion, APAP at a maximal daily dose of 3 g/day (for up to 2 days) or at a daily dose of 1 g/day (for up to 25 days) does not appear to be associated with acute hepatic decompensation. NSAIDs may be associated with acute hepatic decompensation, however we did not find a definite association and this should be clarified by future studies.

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Abbreviations used in this paper

APAP	acetaminophen (<i>N</i> -acetyl-para-aminophenol)
AST	aspartate aminotransferase
CTP	Child–Turcotte–Pugh
INR	international normalized ratio
MELD	Model of End-Stage Liver Disease
NSAIDs	nonsteroidal anti-inflammatory drugs
OTCAs	over-the-counter analgesics

Table 1

Baseline Characteristics of Study Groups

Characteristics	Cirrhotic cases	Cirrhotic controls	Noncirrhotic controls	P
N	91	153	89	
Age, y (range)	55 (24–84)	53 (19–89)	59 (20–91)	.01
Male gender, n (%)	61 (67)	102 (67)	48 (54)	.097
Race, n (%)				.432
Caucasian	78 (86)	125 (82)	67 (75)	
African American	10 (11)	20 (13)	19 (21)	
Other	3 (3)	8 (5)	3 (3)	
Mean arterial pressure, mm Hg (range)	82 (40–123)	91 (68–137)	92 (59–123)	<.001 ^a
Heart rate, bpm (range)	82 (20–121)	76 (53–110)	80 (44–124)	.02 ^b
Etiology of cirrhosis				<.001
Alcoholic (alone or associated with viral), n (%)	49 (54)	40 (26)		
Nonalcoholic, n (%)	42 (46)	113 (74)		
Hepatitis C and/or B, n	28	70		
Cholestatic liver disease (PBC or PSC), n	2	12		
Other, n ^c	12	31		
Total bilirubin, mg/dL (range)	2.6 (0.5–50.9)	1.0 (0.1–6.76)	—	<.001
Albumin, g/dL (range)	2.7 (0.7–4.9)	3.7 (1.7–5.0)	—	<.001
INR (range)	1.70 (1.07–7.13)	1.24 (0.81–1.53)	—	<.001
CTP score (range)	9 (5–15)	6 (5–12)	—	<.001
CTP class, n (%)				<.001
A	7 (8)	107 (70)	—	
B	41 (45)	40 (26)	—	
C	43 (47)	5 (3)	—	
Past cirrhosis decompensation, n (%)	42 (46)	40 (26)	—	.001
Liver medication compliance, %	89	93	—	.1

PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis.

^aSignificantly different between cirrhotic cases and both control groups.

^bSignificantly different between cirrhotic controls and the other 2 groups.

^cIncludes hemochromatosis, autoimmune hepatitis, drug-induced (methotrexate in 1 patient), nonalcoholic steatohepatitis, sarcoidosis, Budd-Chiari, and cryptogenic.

Table 2

Events Leading to Admission in Cirrhotic Patients

Type of decompensation	All cases (N = 91), n (%)	Matched cases ^a (n = 45), n (%)
Hepatic encephalopathy	37 (41)	15 (33)
Ascites	27 (30)	13 (29)
Variceal hemorrhage	21 (23)	17 (38)
Hepatic hydrothorax	7 (7)	4 (9)
Jaundice	5 (5)	2 (4)
Spontaneous bacterial peritonitis	5 (5)	1 (2)
Renal failure	4 (4)	0
Bacteremia	4 (4)	1 (2)

^aPatients that could be subsequently matched by age and CTP class to cirrhotic controls.

Table 3**OTCA Use in Past 30 Days**

	Cirrhotic cases (n = 91)	Cirrhotic controls (n = 153)	Noncirrhotic controls (n = 89)	P
Subjects using, n (%)				
OTCA	32 (35)	80 (52)	62 (70)	<.001 ^a
Acetaminophen	17 (19)	38 (25)	37 (42)	.001 ^b
NSAIDs	15 (16)	48 (31)	30 (34)	.001 ^c
Aspirin	5 (6)	12 (8)	22	
Ibuprofen	5 (6)	35 (23)	9	
Naproxen	5 (6)	4 (3)	1	
Days used, n (range)				.91
Acetaminophen	3 (1–30)	3 (1–30)	3 (1–30)	
NSAIDs				
Aspirin	10 (1–30)	1.5 (1–30)	30 (10–30)	
Ibuprofen	4 (1–21)	3 (1–30)	3 (1–15)	
Naproxen	4 (1–15)	1.5 (1–7)	2	
Amount used in 30 days, g (range)				.32
Acetaminophen	2.0 (0.3–39.0)	2.3 (0.3–24.4)	3.2 (0.3–39.0)	
NSAIDs				
Aspirin	3.2 (0.62–9.75)	1.3 (0.62–58.5)	9.75 (1.22–39)	
Ibuprofen	4.0 (0.5–31.5)	2 (0.4–72)	1.8 (0.4–22.5)	
Naproxen	0.88 (0.22–6.6)	0.36 (0.22–4.6)	0.44	

^aDifferences significant among all groups.^bSignificant difference between noncirrhotic controls and the other 2 groups.^cSignificant difference between cirrhotic cases and both control groups.

Table 4

Alcohol Use in Study Groups

	Cirrhotic cases (n = 91)	Cirrhotic controls (n = 153)	Noncirrhotic controls (n = 89)	P
Patients using alcohol in last month, n (%)	25 (28)	30 (20)	29 (33)	.07
Alcohol used in last month, g (range)	380 (10–4500)	42 (5–3300)	20 (10–900)	<.001 ^a
Days alcohol used in last month per person, median (range)	13 (1–30)	3 (1–30)	2 (1–30)	.001 ^a
Lifetime alcohol use, g (range)	140,640 (240–2,160,000)	175,440 (120–3,817,440)	50,840 (960–2,036,640)	<.001 ^b

^aSignificant difference between cirrhotic cases and both control groups.

^bSignificant difference between noncirrhotic controls and the other 2 groups.

Table 5

Subjects with Alcoholic and Nonalcoholic Etiology of Cirrhosis

	Alcoholic etiology		Nonalcoholic etiology	
	Cirrhotic cases (n = 49)	Cirrhotic controls (n = 41)	Cirrhotic cases (n = 42)	Cirrhotic controls (n = 112)
APAP use	7 (14)	7 (17)	10 (24)	31 (28)
NSAID use	9 (18)	10 (24)	5 (12)	38 (34) ^a
Used alcohol in past month	19 (39)	9 (22)	6 (14)	21 (19)
Amount of alcohol used in last month, <i>g</i>	580 (10–4500)	80 (10–3300) ^b	53 (10–600)	30 (5–600)
Days of alcohol use in last month	20 (1–30)	2 (1–30) ^b	2 (1–30)	3 (1–30)

NOTE. Data are given as n (%) or (range).

^a*P* = .006.^b*P* = .03 compared with patients.

Table 6

Comparison of OTCA and Alcohol Use in Matched Patients

	Matched cirrhotic cases (n = 45)	Matched cirrhotic controls (n = 45)	Matched noncirrhotic controls (n = 45)	P
Age (y)	53 (36–83)	54 (27–80)	60 (20–91)	.202
CTP score	8 (5–13)	8 (5–12)	—	.284
OTCA use	16 (36)	24 (53)	32 (71)	.003
APAP use	10 (22)	15 (33)	21 (47)	.049
NSAID use	6 (14)	11 (24)	13 (29)	.19
Alcohol use in last month	19 (42)	3 (7)	17 (38)	<.001
Amount of alcohol in last month, grams	380 (10–4500)	220 (30–520)	20 (10–900)	<.001
Days of alcohol use in last month	10 (1–30)	7 (2–25)	1 (1–30)	<.001

NOTE. Data are given as n (%) or (range).