

## ACETAMINOPHEN TOXICITY IN AN URBAN COUNTY HOSPITAL

FRANK V. SCHIØDT, M.D., FEDJA A. ROCHLING, M.D., DONNA L. CASEY, B.S., AND WILLIAM M. LEE, M.D.

**ABSTRACT**

**Background** The prevalence and characteristics of acetaminophen-associated liver injury in hospitalized patients are not well defined.

**Methods** We identified patients hospitalized for excessive acetaminophen ingestion at an urban county hospital over a 40-month period (1992 to 1995) and reviewed their medical records to determine the incidence and clinical features of the ingestions and their outcomes.

**Results** Of the 71 patients studied, 50 were classified as having taken acetaminophen during suicide attempts and 21 as having accidentally poisoned themselves while attempting to relieve pain. The suicidal patients had ingested almost twice as much acetaminophen as those in the accidental-overdose group (median, 20 vs. 12 g;  $P=0.009$ ). Among the patients for whom data were available, 63 percent of those in the accidental-overdose group and 25 percent of those in the suicidal group were chronic alcohol abusers ( $P=0.009$ ). The patients in the accidental-overdose group more often had severe liver necrosis (aminotransferase levels,  $>3500$  IU per liter; 52 percent vs. 14 percent;  $P=0.002$ ) and were more likely to have hepatic coma (33 percent vs. 6 percent,  $P=0.006$ ). There were four deaths (19 percent) in the accidental-overdose group and one (2 percent) in the suicidal group ( $P=0.04$ ). Five patients — three in the accidental-overdose group and two in the suicidal group — had ingested 4 g of acetaminophen or less. Acetaminophen ingestion accounted for 12 percent of all patients hospitalized with overdoses (71 of 589) and 40 percent of patients with acute liver failure (10 of 25) during the study period.

**Conclusions** In an urban county hospital, patients hospitalized with acetaminophen toxicity related to accidental misuse had higher rates of morbidity and mortality than those who attempted suicide, even though the latter had taken more acetaminophen. A higher frequency of chronic alcohol abuse among the patients with accidental overdoses may be one explanation. (*N Engl J Med* 1997;337:1112-7.)

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**H**EPATOTOXICITY due to overdoses of acetaminophen (also known as paracetamol) has become an important problem.<sup>1,2</sup> Previous reports have defined two distinct clinical syndromes. When patients attempting suicide ingest large amounts of acetaminophen, acute liver failure associated with multiorgan failure, nephrotoxicity, and occasionally pancreatitis may develop unless antidotes are given.<sup>3,4</sup> This pattern is

the most common cause of acute liver failure in the United Kingdom. A second pattern, apparently more prevalent in the United States, is observed in alcoholic or fasting patients who ingest smaller amounts of acetaminophen only to relieve pain and in whom alcohol use or starvation appears to worsen the liver injury.<sup>1,5-7</sup> Suicidal overdoses have been common in the United Kingdom since the 1970s,<sup>8</sup> and their incidence appears to be increasing in the United States.<sup>9,10</sup> Despite these reports, little information is available on the overall incidence and severity of acetaminophen hepatotoxicity in the United States.

We retrospectively examined the records of patients with acetaminophen toxicity in an urban county hospital over a 40-month period to determine the incidence and clinical profile of acetaminophen-associated liver injury.

**METHODS**

The study group consisted of all patients admitted to Parkland Memorial Hospital, the sole public hospital in Dallas County, Texas (with approximately 40,000 admissions annually), for potential or actual acetaminophen hepatotoxicity between January 1, 1992, and April 30, 1995. Since the hospital does not perform liver transplantation, no patients were referred for that purpose, and no patients required transplantation.

The patients' medical records were identified and retrieved in two ways. First, we used coding software (Code 3 N-coder, 3M, Minneapolis) to search the data base for all patients coded as having hepatic necrosis (a category that included acute liver failure), drug overdose, or alcoholic hepatitis. Patients defined clinically as having typical alcoholic hepatitis were excluded from further study.<sup>11</sup> Second, we reviewed the records of all patients in whom acetaminophen levels greater than 10 mg per liter were measured. We confirmed that a patient had had substantial acetaminophen ingestion if the ingestion of a large amount of acetaminophen was reported unequivocally by the patient or a family member, if the patient had a blood acetaminophen level greater than 10 mg per liter, or if the patient had serum aminotransferase levels exceeding 3500 IU per liter, a finding previously associated with acetaminophen toxicity.<sup>4,7</sup> Patients who did not meet these criteria included those in whom elevated serum aminotransferase levels were found but substantial acetaminophen ingestion could not be adequately confirmed and those in whom a second cause, such as acute hepatitis A or B, was considered to account at least in part for the clinical picture.

Our primary objectives were fourfold: to document the incidence of acetaminophen toxicity during a defined study period in an urban county hospital that does not serve as a transplantation center; to analyze the clinical, biochemical, and epidemiologic data recorded for these patients, all of whom were hospitalized specifically for this problem; to establish the cost of hospitaliza-

From the Liver Division, Department of Internal Medicine, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd., Dallas, TX 75235-9151, where reprint requests should be addressed to Dr. Lee.

tion related to acetaminophen toxicity; and to assess the outcome with regard to morbidity and mortality. Data were collected on age, sex, race or ethnic group, dates of admission and discharge, diagnosis, cost of hospitalization, amount of acetaminophen ingested (including that in all compound preparations), the reason for the ingestion, the timing of the ingestion in relation to presentation at the hospital, and the timing of antidote therapy with acetylcysteine. Data on costs were obtained from the hospital billing office and consisted of the total cost of each patient's admission as calculated for billing purposes. In addition, laboratory data included acetaminophen levels and admission, peak, and discharge values for aspartate aminotransferase (normal, 5 to 35 IU per liter), alanine aminotransferase (normal, 7 to 56 IU per liter), bilirubin (normal, 0.2 to 1.3 mg per deciliter [3.4 to 22 μmol per liter]), creatinine (normal, 0.7 to 1.7 mg per deciliter [61 to 150 μmol per liter]), and prothrombin time (normal, 11.0 to 13.1 seconds). Precise assessments of alcohol intake, the amount of acetaminophen ingested, and nutritional state were not always possible. When complete data were unavailable, best estimates were made. When there was a suspicion of acetaminophen ingestion but residual doubt because of poor documentation by the medical staff, the patient was excluded from further study.

**Statistical Analysis**

In the analysis of quantitative data, Student's unpaired t-test was used to compare the study groups with regard to variables with normal distributions (such as age), and the Mann-Whitney U test was used for variables with non-normal distributions (such as the serum bilirubin level).<sup>12</sup> In the analysis of qualitative data, Fisher's exact test was used for categorical variables (such as grades of hepatic coma), and the chi-square test was used to test for group differences when there were more than two possible values (such as ethnic distribution). Data are given as means ±SD, medians and ranges, or both. All the analyses were two-tailed. P values of less than 0.05 were considered to indicate statistical significance.

**RESULTS**

We initially considered 80 patients to have had evidence of acetaminophen hepatotoxicity according to our criteria. Nine patients were excluded, either because there was not enough information to confirm their clinical status or because other causes were also present, leaving 71 patients who were considered further. Of these, 50 patients (70 percent) had attempted suicide by overdose and the remaining 21 had accidental toxic effects from acetaminophen ingestion while seeking relief from pain. The study groups are compared in Tables 1 and 2. The suicidal patients tended to be younger than those in the accidental-overdose group and included greater proportions of whites and Asians, whereas the accidental-overdose group included predominantly blacks and Hispanics, with a comparatively small proportion of whites. Each group contained more women than men (overall, 48 vs. 23). The suicidal patients had ingested almost twice as much acetaminophen as those in the accidental-overdose group (median, 20 vs. 12 g; P=0.009). Five patients were considered to have potential or actual toxic effects after the ingestion of 4 g or less in a 24-hour period. Acute alcohol ingestion was common in both groups, whereas chronic alcohol abuse was significantly more prevalent in the accidental-overdose group. Approx-

**TABLE 1. DEMOGRAPHIC CHARACTERISTICS OF 71 PATIENTS WHO INGESTED OVERDOSES OF ACETAMINOPHEN, EITHER ACCIDENTALLY OR IN A SUICIDE ATTEMPT.**

CHARACTERISTIC	ACCIDENTAL OVERDOSE (N=21)	SUICIDAL OVERDOSE (N=50)	P VALUE
Age — yr			
Mean ±SD	34±10	29±13	
Median	36	26	0.12
Range	16–54	14–83	
Sex — F/M	11/10	37/13	0.10
Race or ethnic group			0.009*
Asian	0	4	
Black	11	9	
Hispanic	4	9	
Native American	1	0	
White	5	28	
Acetaminophen dose — g			
Mean ±SD	11±7	24±22	
Median	12	20	0.009
Range	2–30	3–125	
Acetaminophen dose ≤4 g — no. (%)	3 (14)	2 (4)	0.15
Ethanol ingestion — no./no. studied (%)			
Acute†	8/18 (44)	14/36 (39)	0.77
Chronic‡	12/19 (63)	11/44 (25)	0.009
Concurrent intoxication — no. (%)§	6 (29)	17 (34)	0.78
Intravenous drug abuse — no. (%)	4 (19)	13 (26)	0.76

\*Chi-square = 13.6, 4 df.

†These values could not be determined in 17 patients.

‡These values could not be determined in eight patients.

§Compound preparations containing acetaminophen were often ingested alone or together with other preparations. In such cases, the total amount of acetaminophen is shown as the ingested dose. Use of the following brand-name drugs was recorded for the study patients: Excedrin (four patients), Darvocet (three), Tylenol #3 (three), Vicodin (two), and Lortab, Fiorcet, Tylenol PM, and Tylenol Sinus (one each). Other medications ingested along with acetaminophen included doxepin, hydrocodone, Somnex, alprazolam, captopril, diphenhydramine, chlorpromazine, glyburide, glipizide, Dyazide, nifedipine, and pseudoephedrine.

imately one third of each group had ingested compounds such as Vicodin (hydrocodone plus acetaminophen) and Darvocet (propoxyphene plus acetaminophen), and other tranquilizers and sedatives had commonly been taken also.

Table 2 shows clinical and laboratory variables and data on outcomes. The accidental-overdose group had more overall liver and kidney injury, as indicated by elevated levels of aminotransferases and creatinine, respectively, despite lower doses of acetaminophen. The highest level of aspartate aminotransferase reached was 34,720 IU per liter in a patient with accidental overdose, although one suicidal patient also had a very high level (15,890 IU per liter). Acetylcysteine therapy was given to 56 patients (79 percent), with no difference between groups. Of the five patients who died, four had received acetylcysteine; this treatment was not given to the fifth be-

**TABLE 2.** CLINICAL VARIABLES PERTAINING TO THE ACCIDENTAL AND SUICIDAL OVERDOSES OF ACETAMINOPHEN IN THE STUDY PATIENTS.\*

VARIABLE	ACCIDENTAL OVERDOSE (N=21)	SUICIDAL OVERDOSE (N=50)	P VALUE
History available — no. (%)	17 (81)	43 (86)	0.72
Presentation >24 hr after overdose	9/14 (64)	5/35 (14)	0.001
— no./no. studied (%)†			
Peak acetaminophen — mg/liter			
Mean ±SD	39±53	145±101	
Median	7	126	<0.001
Range	1–155	8–460	
Peak acetaminophen >10 mg/liter	7/15 (47)	46/49 (94)	<0.001
— no./no. studied (%)‡			
Peak ALT — IU/liter			
Mean ±SD	2557±3061	1384±2918	
Median	1964	26	0.003
Range	9–12,700	6–10,550	
Peak AST — IU/liter			
Mean ±SD	7430±10,309	1501±3555	
Median	3490	31	0.001
Range	19–34,720	11–15,890	
Peak ALT or AST — no. (%)			
>1000 IU/liter	13 (62)	10 (20)	0.002
>3500 IU/liter	11 (52)	7 (14)	0.002
Peak prothrombin time — sec			
Mean ±SD	25.7±18.5	18.0±12.4	
Median	18.0	13.8	0.04
Range	11.7–76.1	11.4–71.5	
Peak serum bilirubin — mg/dl			
Mean ±SD	12.0±15.1	1.4±2.4	
Median	4.2	0.7	0.004
Range	0.2–51.6	0.2–12.9	
Peak serum creatinine — mg/dl			
Mean ±SD	2.6±2.6	1.0±0.3	
Median	1.3	0.9	0.05
Range	0.6–9.4	0.5–1.7	
No. of criteria met§			0.27¶
1	9	12	
2	10	30	
3	2	8	
Acetylcysteine therapy — no. (%)	16 (76)	40 (80)	0.76
Hepatic coma — no. (%)	7 (33)	3 (6)	0.006
Death — no. (%)	4 (19)	1 (2)	0.04
Hospital stay — days			
Mean ±SD	9±13	4±4	
Median	4	3	0.60
Range	1–51	1–23	
Cost — dollars			
Mean ±SD	19,086±27,473	8,487±6,720	
Median	5,897	6,899	0.51
Range	1,019–81,558	632–44,976	

\*ALT denotes alanine aminotransferase, and AST aspartate aminotransferase. To convert values for acetaminophen to micromoles per liter, multiply by 6.62. To convert values for bilirubin to micromoles per liter, multiply by 17.1. To convert values for creatinine to micromoles per liter, multiply by 88.4.

†The precise time of the overdose was not available for 22 patients.

‡Peak acetaminophen levels were not determined in seven patients.

§The three criteria used to establish the likelihood of an overdose or toxic effects of acetaminophen were as follows: an unequivocal report by the patient or a family member of a large ingestion of acetaminophen, a blood acetaminophen level greater than 10 mg per liter, and serum aminotransferase levels exceeding 3500 IU per liter.

¶Chi-square = 2.6, 2 df.

||Data on cost were derived from billing statements on each patient's hospitalization that were obtained from the hospital billing office. Such statements were available for 63 patients, 18 in the accidental-overdose group and 45 in the suicidal group.

cause the patient entered the hospital seven days after the acetaminophen ingestion.

#### Suicidal Overdoses

Of the 50 patients whose overdoses were considered to constitute suicide attempts, 43 (86 percent) had histories consistent with such an attempt, whereas the remaining 7 had either taken large amounts of acetaminophen as an angry gesture (5 patients) or denied having suicidal ideation but had very high acetaminophen levels (2). This group had less severe toxic effects, with 31 patients (62 percent) never having abnormal aminotransferase levels. Ten patients (20 percent) had substantial toxic effects (alanine or aspartate aminotransferase, >1000 IU per liter) despite the use of acetylcysteine in most cases. The demographic features of this subgroup of patients were similar to those of the other suicidal patients, except that among the patients with substantial toxic effects the median total dose of acetaminophen ingested was higher (42 vs. 19 g,  $P < 0.005$ ), a majority of patients were chronic alcohol abusers (67 percent vs. 14 percent,  $P < 0.004$ ), and the patients presented for treatment later (median, 16 hours, as compared with 5 hours for the remaining patients;  $P < 0.003$ ).

#### Accidental Overdoses

Among the 21 patients who were considered not to have had suicidal intent, in each case a specific history of attempted relief from pain was elicited, suicidal ideation was denied, and the patient presented significantly later for hospitalization. Acetaminophen ingestion beyond the amount recommended on the package label for adults in the United States (4 g every 24 hours) occurred in 18 patients, although only 7 patients (33 percent) had ingested more than 10 g, and the total dose was typically ingested over a period of more than 24 hours. The reasons given for seeking relief from pain included toothache (five patients), abdominal pain (four), and headache (three), among other reasons. Only five patients were admitted to the hospital because of a specific history of excess acetaminophen ingestion; the majority had abnormal aminotransferase levels or prothrombin times that mandated their admission. Measures of severity of illness (aminotransferase levels, bilirubin levels, and prothrombin time) were all more pronounced in the accidental-overdose group than in the suicidal group (Table 2). Hepatic coma and death were more frequent in the accidental-overdose group. Median hospital costs and length of stay were similar in the two groups.

During the period of the study, 589 patients were listed in the hospital data base as having been admitted for drug overdoses, including the patients ingesting excess acetaminophen, and in 25 patients (including 10 in this series) acute liver failure was di-

agnosed according to the standard criteria of hepatic coma plus coagulopathy.<sup>10</sup> Thus, acetaminophen ingestion accounted for 12 percent of all patients with overdoses (71 of 589) and 40 percent (10 of 25) of patients with acute liver failure during the same period. The total population of Dallas County is approximately 1 million. On the basis of demographic studies of the county, our hospital is estimated to provide care to 40 percent of this population. Given these data, the annual incidence of potential or actual acetaminophen toxicity requiring hospitalization was estimated at 53 (95 percent confidence interval, 39 to 67) per million.

#### DISCUSSION

In evaluating the overall experience with acetaminophen in an urban hospital, we found one group of patients with suicidal ingestions and another group who were admitted with established toxic effects of acetaminophen. The latter had ingested smaller amounts of acetaminophen than the former, usually for pain relief, and they had frequent evidence of alcohol abuse. Low or undetectable levels of acetaminophen ( $\leq 10$  mg per liter) were found in 8 of 15 patients in the accidental-overdose group (53 percent), as compared with only 3 of 49 patients in the suicidal group (6 percent) (Table 2), presumably because of late presentation or multiple small ingestions over time. Nevertheless, the accidental-overdose group had higher morbidity and mortality than the suicidal group, partly because no antidote is maximally effective if given more than 24 to 48 hours after the ingestion of the toxic substance. Since accurate knowledge of a single time when the ingestion occurred was frequently lacking for these patients, using a nomogram to determine the need for therapy is inappropriate. Symptoms, signs, and laboratory evidence of severe hepatotoxicity developed in the patients who had accidental overdoses, with nearly two thirds having aminotransferase levels higher than 1000 IU per liter and acute liver failure developing in one third. This group may not have included all patients with toxic effects, since patients with subclinical liver damage might not have come to the hospital. This may explain the high frequency of severe toxic effects in the patients who were admitted. Population-based rates of adverse events not requiring hospitalization cannot be calculated from the type of data we collected.

Despite the very large amounts of acetaminophen consumed, remarkably few toxic effects were observed in the patients who made suicide attempts, probably because of their early presentation for treatment. This more favorable outcome underscores the importance of the prompt use of acetylcysteine.<sup>4,13-16</sup> Because acetaminophen-related admissions at our hospital are relatively frequent, our staff may administer antidotes more readily than physicians at smaller hospitals where such cases occur less frequently.<sup>17</sup>

The experience at other centers would also suggest that few patients die or need liver transplantation after ingesting acetaminophen in a suicide attempt. We found that chronic alcohol abuse, the ingestion of higher doses of acetaminophen, and late presentation were all more frequent in the subgroup of suicidal patients with severe hepatic necrosis. These same risk factors for severe acetaminophen toxicity among suicidal patients have been reported from Australia.<sup>18</sup> Even when acute liver failure develops because of a suicidal overdose of acetaminophen, patients generally have a good prognosis, with only a small number requiring liver transplantation or dying.<sup>3,8,18,19</sup>

Acetaminophen is metabolized principally through glucuronidation and sulfation; when the drug is taken at therapeutic doses, only a small portion is oxidized by cytochrome P450 2E1. When the quantity ingested exceeds the capacity for sulfation and glucuronidation, an avidly electrophilic compound, *N*-acetyl-*p*-benzoquinoneimine (NAPQI), is formed by P450 2E1, causing covalent bonding with cell proteins and DNA and resultant liver injury. This injury can be prevented if NAPQI is detoxified by conjugation with glutathione to yield mercapturic acid, a harmless water-soluble product excreted by the kidney.<sup>20</sup> Depletion of glutathione as a result of starvation and chronic alcohol ingestion increases toxicity. Acetylcysteine replenishes glutathione, thus protecting against acetaminophen-induced injury.<sup>13,14,21-24</sup> In addition, the induction of the P450 2E1 enzyme by chronic exposure to ethanol increases toxicity, although the enzyme may also be inhibited in the setting of acute ethanol intoxication.<sup>21,22</sup> Despite its uncertain efficacy when administered more than 48 hours after the acetaminophen ingestion, acetylcysteine is recommended for late use by most authors.<sup>8,15</sup> Not all patients in our accidental-overdose group had chronic ethanol ingestion. Other factors may increase toxic effects in some patients. Our study has not established a specific synergy between acetaminophen and alcohol.

More than 200 formulations containing acetaminophen are available in the United States. The foremost brand of acetaminophen, Tylenol (McNeil Products, Fort Washington, Pa.), currently carries a warning on the package about the ingestion of more than 4 g (eight 500-mg tablets) in a 24-hour period by adults and the use of the product in conjunction with other acetaminophen-containing compounds. The package label also suggests that people consuming more than three alcohol-containing drinks should consult their doctors. Most other preparations of acetaminophen are sold with similar warnings. The patients in the accidental-overdose group had frequently exceeded the recommended doses. The reasons given included too-frequent dosing (such as every two hours) or overdosing (>1 g per dose) due

to persistent pain, the ingestion of compounds the patient did not know contained acetaminophen, the ingestion of multiple preparations of acetaminophen simultaneously, ignorance of toxic effects in general or of the dosing limit, and clouded sensorium due to alcohol. We could not accurately determine whether the patients had been fasting; this has been shown to be an important cofactor for acetaminophen toxicity in animals and people.<sup>6,21</sup>

Substantial toxic effects were observed in five patients who apparently ingested 4 g of acetaminophen or less in a 24-hour period — three in the accidental-overdose group and two in the suicidal group — and they were possibly also related to fasting, excessive alcohol consumption, genetic differences in P450 constitution, or a combination of these.<sup>23</sup> Our findings differ from those in the United Kingdom, where no definite association between chronic alcohol intake and toxic effects of acetaminophen has been recognized.<sup>8,24</sup> Since patients who ingest acetaminophen to commit suicide seem more prevalent in the United Kingdom, these differences may reflect an overwhelming preponderance of suicidal patients; however, acetaminophen toxicity associated with alcohol abuse has been reported repeatedly from Australia, as well as in many U.S. case reports.<sup>1,2,5,7,18,20,25,26</sup>

The observation that low doses of acetaminophen — those only slightly above, and even occasionally within, the therapeutic range — were associated with severe hepatotoxicity in patients with accidental ingestions implicates cofactors, such as alcohol and starvation, but does not prove the link. A formal case-control study of alcohol ingestion and acetaminophen toxicity has yet to be performed. However, the presence of extremely high aminotransferase levels in virtually all the patients described, including those we studied, distinguishes this clinical picture from that of alcoholic hepatitis, alcoholic cirrhosis, most forms of viral hepatitis, and other forms of acute liver injury.<sup>5</sup>

Despite its apparent overall safety, acetaminophen was the most frequent cause of acute liver failure at our hospital, accounting for five deaths during the study period. Excessive ingestion of acetaminophen should be considered in the setting of suicidal overdoses of medication and in patients with very high aminotransferase levels. Acetaminophen, the most commonly used pain reliever, has substantial potential for fatal hepatotoxicity when it is misused through accidental overdose or in suicide attempts. The lack of awareness of these hazards on the part of both the public and some physicians<sup>17</sup> suggests the need for greater education.

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