

Research

Acetaminophen toxicity: suicidal vs accidental

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Abstract

Introduction Acetaminophen toxicity, which can lead to hepatotoxicity, is a burden on our health care system and contributes significantly to intensive care unit admissions and cost of hospitalization. The aim of our study was to determine the epidemiology of various types of acetaminophen poisoning and analyze their outcome compared with their admission characteristics.

Methods We identified 93 consecutive patients, hospitalized for acetaminophen toxicity over a 52-month period from 1996 to 1999 in our urban county hospital. Retrospective case-control analysis was carried out using the data obtained from the medical records.

Results Acetaminophen accounted for 7.5% of all cases of poisoning admitted during this period. Of the 93 patients, 80 were classified as suicidal and 13 had accidentally poisoned themselves in an attempt to relieve pain. The ratio of females to males was found to be 2:1. Of the 93 patients studied, 88 were admitted to the intensive care unit for initial 24–48 hours of monitoring. Peak acetaminophen levels were higher in the suicidal overdose group (mean 121.7 ± 97.0 mg/l vs 64.5 ± 61.8 mg/l, $P < 0.05$) than in the accidental group. In spite of this, peak aminotransferase levels >1000 IU/l were more often seen in the latter (39% vs 12%, $P < 0.05$). Hepatic coma and death were seen more often in the accidental overdose group (15% vs 0%, $P < 0.05$). Interestingly chronic alcohol abuse was also more frequent in the accidental overdose category (39% vs 18%, $P = 0.05$).

Discussion Although the peak acetaminophen level in the suicidal group was significantly higher, cases of therapeutic misadventure had higher rates of morbidity and mortality. Peak acetaminophen levels correlate poorly with hepatic dysfunction, morbidity and mortality.

Conclusion We recommend that the patients with suicidal acetaminophen overdose, without any concomitant poisoning, can safely managed on the medical floors.

Keywords acetaminophen toxicity, epidemiology, hepatotoxicity, therapeutic misadventure

Introduction

Acetaminophen gained widespread popularity in the 1960s as a less toxic, analgesic antipyretic agent than aspirin. Ironically, acetaminophen is now the second leading cause of toxic drug ingestions in the United States [1]. Acetaminophen toxicity is thus a real burden on our health care system, and hepatotoxicity due to acetaminophen overdose has become an important problem [2,3].

There are two distinct clinical syndromes described in literature. One is the 'garden variety', wherein the patients ingested large amounts of acetaminophen with a suicidal intent [4,5]. The other pattern is seen in chronic alcoholics who ingest smaller amounts of acetaminophen in an attempt to relieve pain [2,6–8]. Some cases of acetaminophen overdose have been described as parasuicidal, where the attempted suicide is more of a gesture than an act of lethal

intent. The aim of our study was to determine the epidemiology of various types of acetaminophen poisoning and analyze their outcome compared with their admission characteristics.

Methods

This study was conducted at Nassau University Medical Center (East Meadow, NY, USA) which represents an urban county hospital. Computer associated search was undertaken of all admission records from January 1996 to April 1999. The records of all the patients with a discharge diagnosis of acetaminophen overdose were analyzed. Patients who were not admitted to the hospital after being assessed in the emergency room were excluded from this study. We included patients who had a history of acetaminophen ingestion reported by either the patient or the family. We went on to confirm that the patient had substantial acetaminophen ingestion by history, blood acetaminophen level >10 mg/l, or serum aminotransferase level >1000 IU/l. Two out of three of these conditions had to be met for a case to be included in our study. Patients who had elevated serum aminotransferase levels but in whom substantial acetaminophen ingestion could not be adequately confirmed were excluded from the study. Chronic alcohol abuse was defined by the Diagnostic and Statistical Manual of Mental Disorders 4th Edition (DSM-IV) criteria [9].

All of the patients with suicidal overdose were admitted to the intensive care unit. For the patients with accidental acetaminophen ingestion, the triage was based on their clinical condition. There was a standard management plan for all the patients, as suggested by the National Poison Control Center. Most of the patients were observed for 24 hours in the intensive care unit before being transferred to the medical floor.

The following information was recorded: age; sex; race; acetaminophen dose; reason for ingestion; history of alcohol abuse or concurrent intoxication; time to presentation to the emergency room since ingestion; and *N*-acetylcysteine therapy. The laboratory data included peak acetaminophen level, peak aminotransferase level, prothrombin time, serum bilirubin, and serum creatinine. Using the International Classification of Diseases Ninth Revision (ICD-9) code [10], the total number of cases of poisonings admitted during the same time period was determined to calculate the prevalence of acetaminophen toxicity.

Statistical analysis

The database used for recording the information was Microsoft Access 6.0. Quantitative data was analyzed using the Students unpaired *t*-test and the Mann-Whitney rank sum test. Analysis of qualitative data was done using the Fisher exact test and the chi-square test. Statistical analysis was performed using Microsoft Excel 6.0.

Results

We identified 100 patients who had evidence of acetaminophen toxicity according to our criteria. Four patients had

Table 1

Characteristics of patients with acetaminophen overdose			
Characteristic	Accidental overdose (n = 13)	Suicidal overdose (n = 80)	<i>P</i> value
Age (years)			
Mean ± SD	35.4 ± 21.84	27 ± 15	< 0.05
Median	36	26	
Range	1-88	12-75	
Sex (n)			0.06
Female	5	54	
Male	8	26	
Race (n)			NS
Asian	0	5	
African American	3	13	
Hispanic	0	8	
White	10	54	
Chronic alcohol abuse (n [%])	5 (39)	15 (18)	0.10
Concurrent intoxication (n [%])	3 (23)	36 (45)	0.20

NS, not significant.

to be excluded, because acetaminophen did not appear to be the culprit for their clinical state. Three others were excluded because they presented with another comorbid condition that could have been responsible for their hepatic profile. None of the patients who were excluded died during their hospitalization.

Acetaminophen accounted for 7.5% of all cases of poisoning admitted during this period. Of the 93 patients, 80 were classified as suicidal based on psychiatric evaluation, and 13 had accidentally poisoned themselves in an attempt to relieve pain. We could not identify any patients with parasuicidal acetaminophen toxicity. The causes of chronic pain in the accidental overdose group were toothache, chronic backache, or headache. Eighty-eight of the 93 patients were admitted to the intensive care unit for first 24-48 hours monitoring.

Table 1 shows that the patients with suicidal ingestion tended to be younger than the accidental group. Female to male ratio was 2:1, with a preponderance of whites in both the groups. Chronic alcohol intake was more prevalent in the accidental overdose subgroup.

It is evident that, although the peak acetaminophen level was higher in the suicidal subgroup (mean 121.7 ± 97.0 vs 64.5 ± 61.8 mg/l, *P* < 0.05), a peak aminotransferase level >1000 IU/l was seen more frequently in the patients with accidental overdose (39% vs 12%, *P* < 0.05) (Table 2). The renal function was overall unaffected and not significantly different between the two groups (data not shown). Morbidity and mortality was higher in the accidental subgroup. There were only two deaths, both in the accidental group; one of whom had a

Table 2**Clinical variables seen in the suicidal and accidental overdose groups**

Variable	Accidental overdose (n = 13)	Suicidal overdose (n = 80)	P value
Presentation >24 hours after overdose (n/n studied [%])	6/9 (66)	7/55 (13)	< 0.001
Peak acetaminophen (mg/l)			< 0.050
Mean ± SD	64.5 ± 61.8	121.7 ± 97.0	
Median	49	99	
Range	0–184	0–439	
Peak acetaminophen <10 mg/l (n [%])	5 (38)	8 (10)	NS
Peak ALT (IU/l)			0.070
Mean ± SD	1386 ± 1918	580 ± 1836	
Median	187	30	
Range	30–5584	30–10356	
Peak AST (IU/l)			0.070
Mean ± SD	1330 ± 2697	504 ± 1708	
Median	114	30	
Range	30–9794	30–10773	
Peak aminotransferase >1000 IU/l (n [%])	5 (39)	10 (12)	< 0.050
Peak prothrombin time (seconds)			< 0.050
Mean ± SD	15.6 ± 7.4	12.7 ± 2.1	
Median	12	12	
Range	12–35	12–25	
Peak serum bilirubin (mg/dl)			< 0.050
Mean	3.8 ± 5.5	1.3 ± 1.3	
Median	1	1	
Range	1–5	1–10	
N-acetylcysteine therapy (n [%])	8 (62)	59 (73)	0.500
Hepatic coma (n [%])	2 (15)	0 (0)	< 0.050
Death (n [%])	2 (15)	0 (0)	< 0.050
Length of stay in hospital (days)			< 0.010
Mean	6.4 ± 6.1	3.9 ± 2.7	
Median	4	3	
Range	1–17	1–17	

history of chronic alcohol abuse. N-acetylcysteine therapy was given to 62% of the patients in the accidental group, compared to 73% in the suicidal overdose group. The hospital stay was higher in the accidental overdose group (mean 6.4 ± 6.1 days vs 3.9 ± 2.7 days, $P < 0.01$).

Discussion

This study did not take the dose of acetaminophen ingested into consideration due to several reasons. Accurate dose estimations could not be made in the accidental group because many of these patients had inadvertent ingestion of acetaminophen in more than one form over several days. The other problem we faced was that some patients in the accidental group were unaware of the presence of acetaminophen in some over-the-counter drugs. About 40% of the patients in the suicidal group could not give an accurate history about the dose of acetaminophen ingested. A substantial number of patients in the suicidal group were drowsy and sedated due to other concomitant ingestions. Moreover,

most of the studies in the literature fail to demonstrate any clear-cut, direct relationship between acetaminophen dose and hepatotoxicity [6]. Low acetaminophen levels (<10 mg/l) were found in 38% patients in the accidental group, compared to 10% in the suicidal overdose group. This is probably because these patients presented late, and they had ingested small doses over a prolonged period.

Surprisingly, the morbidity and mortality were higher in the accidental overdose group than the suicidal group (15% vs 0%, $P < 0.05$). There are two reasons for this. First, these patients present late and sometimes the diagnosis is delayed, both of which hinder optimal antidotal treatment. The second reason could be the increased chronic alcohol use among the accidental group (39% vs 12%, $P < 0.05$). However, the data on the amount of alcohol, duration of intake, or interval between intake of alcohol and acetaminophen are subject to recall bias, withholding of information by the patient, or non-responsive state of the patient on presentation.

The presumed basis for the potentiation of acetaminophen-induced hepatotoxicity by chronic ethanol ingestion has been amply discussed [11–14]. Elegant studies performed in the early 1970s [15] established that acetaminophen, taken in therapeutic doses, is metabolized by the liver through two pathways. Most of the drug (80–90%) is conjugated with either glucuronic acid or sulphates, yielding the nontoxic conjugates that are excreted by the kidney. A small proportion (5%) is metabolized to a reactive electrophilic intermediate by the cytochrome P-450 system. This metabolite is rendered nontoxic by conjugation with glutathione to form mercapturic acid and related conjugates that are also excreted in the urine. If the drug is taken in excessive doses, an augmented amount is converted by cytochrome P-450 to the highly reactive, toxic intermediate metabolite [15,16]. It then may reach a level that overwhelms the protective mechanism of glutathione conjugation and ultimately, through covalent binding to hepatocyte proteins, leads to hepatocellular necrosis [17].

Therapeutic doses of acetaminophen have the potential of producing liver damage if they are associated with circumstances that enhance the activity of the P-450 system leading to increased production of toxic metabolite, or that interfere with the protective mechanism by depleting the available glutathione. Ethanol can potentiate damage due to both of these reasons [11–14].

In the present study 6/9 (66%) patients in the accidental overdose group and 7/55 (13%) in the suicidal overdose group presented to the emergency room more than 24 hours after the overdose. *N*-acetylcysteine therapy was given to 62% of the patients in the accidental group, compared to 73% patients in the suicidal group. Treatment with *N*-acetylcysteine has been very successful in preventing or ameliorating hepatic injury after suicidal acetaminophen overdose. However, the benefit of *N*-acetylcysteine in the syndrome of acetaminophen injury as a therapeutic misadventure is not clearly defined. The final outcome in the case of accidental overdose is dependent on a multitude of factors, and thus a large number of cases will be required for multivariate analysis to identify the role of *N*-acetylcysteine. As the efficacy of *N*-acetylcysteine as an antidote decreases after eight hours, the treatment must be started immediately following all potentially toxic doses of acetaminophen (>10 g). However, a large retrospective trial indicated that *N*-acetylcysteine therapy decreased the incidence of hepatotoxicity when administered up to 24 hours post overdose [18]. Patients, who have an increased susceptibility to acetaminophen toxicity, particularly alcoholics, should be considered for *N*-acetylcysteine therapy at plasma levels that are half of those indicated in the standard graph [19,20]. In addition, patients with accidental overdose acquired over a number of hours should be still considered for treatment, because in these cases plasma levels are unreliable in predicting hepatotoxicity.

Our study also showed that, although patients with suicidal overdose had higher peak acetaminophen levels than the accidental overdose group, the peak aminotransferase level (>1000 IU/L) was more often seen in the accidental overdose group (39% vs 12%, $P < 0.05$). The suicidal overdose patients with high levels of liver enzymes more often had a history of chronic alcohol abuse and they presented late. Similar results have been reported in an Australian study [21]. Even when acute hepatic failure develops because of suicidal overdose of acetaminophen, these patients have a good prognosis in terms of liver transplantation and death. [4,21–23]. In fact, none of our patients in the suicidal overdose group died or had to be referred for transplantation. In contrast to this, in the accidental overdose group 2/13 patients developed fulminant hepatic failure leading to hepatic coma and ultimately to death. Thus peak acetaminophen levels correlate poorly with hepatic dysfunction, morbidity and mortality.

The number of days of hospitalization was higher in the accidental group. There are numerous studies which have shown that the total cost of treating a patient in the intensive care unit in the US is approximately \$25,000–35,000 per day [24,25]. It is a tradition in many hospitals in the country to admit patients with acetaminophen overdose to critical care units. In our study, out of the 80 patients in the suicidal group, 75 were admitted to the intensive care unit, whereas all the 13 patients in the accidental overdose group were admitted to this unit. Because of their benign clinical course, we recommend that patients with suicidal acetaminophen overdose can be safely managed on the medical floors unless there is a history of chronic alcohol abuse or other concomitant poisonings. In our hospital this would translate to a cost saving of at least \$500,000 per year.

Conclusion

In summary, acetaminophen poisoning continues to remain a significant reason for hospital admissions among young adults. Peak acetaminophen levels correlate poorly with the clinical course. The admission of the patients to the intensive care unit or ward should be determined by the degree of derangement of their clinical parameters. Patients with suicidal overdose and no history of chronic alcohol use do not need be admitted to the intensive care unit. This excludes patients for whom there is any doubt about the history of chronic alcohol abuse and those who have accidentally poisoned themselves. These are the patients who have an unfavorable clinical course and should be monitored in a critical care setting.

Competing interests

None declared.

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