Acetaminophen Self-Poisoning: Suicidal and Accidental

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Objective: Acetaminophen is an over-the-counter drug in Iran. Intentional and accidental poisoning with this drug is one of the most frequent causes of admission to our center. We studied the outcome of poisoning with this drug in our hospital.

Methods: Over a two-year period from January 2005 to January 2007, 85 patients who were admitted to Sina Hospital for acute acetaminophen poisoning, were followed up. Identification and outcome of patients were according to a physical examination, medical history, lab data and duration of hospital stay.

Results: Acute acetaminophen poisoning occurred in both genders and all age groups. Approximately 64 percent of patients were female. Children had minimal involvement and were usually accidental poisoning type (98%). In adults, admissions were more likely to be due to suicide attempts rather than accidental poisoning. The majority of cases were in hepatotoxic dose, but clinical courses were mild. Patients, who had acutely ingested more than 150 mg/kg or predicted to be hepatotoxic due to impaired liver function testes, had a longer hospital stay but in spite of this, we did not have any mortality.

Conclusion: Overdose with acetaminophen in adults was often indications of suicidal behavior, and in children was usually of accidental type. The outcome was generally good in spite of common acetaminophen poisoning.

Declaration of interest: None.

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Introduction

Acetaminophen is one of the most common agents implicated in accidental or intentional poisonings(1). Acetaminophen is the most commonly used antipyretic and analgesic drug; excluding combination preparations, approximately 1.5 billion tablets are sold annually in Canada. Between 1997 and 2002, the adjusted incidence of acetaminophen overdose was 46 per 100,000 populations. Although other Canadian incidence data are lacking, this figure is approximately double than reported in the United States (2). Acetaminophen toxicity is one of the most frequent causes of acute liver failure in both United States and the United Kingdom (3,4). It should be noted that reports from other eastern countries, i.e., Singapore and Malaysia were better (3,5). In Iran, acetaminophen is an over-the-counter medication in several different formulations and strengths. Overdose with over-the-counter drugs are often indications of suicidal behavior, and one of the most common medications involved in overdose is acetaminophen. This drug has a high prevalence exposure rate among drugs and chemicals, administered to admitted patients in the Sina Teaching Hospital Toxicology Ward, Tabriz, Iran. Tabriz is a city in Northwest of Iran, which has a population of approximately 2 million people. Approximately, 70% of total hospital admissions in Sina Hospital were due to drug intoxication in this particular city. This article reveals the characteristics and outcomes of this type of poisoning over a two-year period.

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Materials and Methods

We studied all patients with acute

acetaminophen poisoning, who were admitted to Sina Hospital during January 2005 to January 2007. All history, physical examinations and paraclinical findings were recorded closely by a single physician. Patients poisoned by a single drug (acetaminophen) enrolled in this study and multi-drug poisonings or patients with previous underlying problems (hepatic, renal, cardiac, and gastrointestinal) were excluded. Patients were followed up during their hospitalization. Demographic parameters, doses, blood level, type of treatment, and outcomes from admitted patients were collected and arranged in tables for final analyses. Hepatotoxicity likelihood was predicted based on blood drug level. The blood drug level measured by our laboratory and hepatotoxicity prediction was determined according to Rumack-Matthew Nomogram (6). This is an assessment to determine the effect of the drug on the liver. The test measures blood levels of acetaminophen relative to the time of ingestion of the medication. The best indicator of acetaminophen toxicity is measurement of the drugs half-life by analyzing the blood drug level taken 6 hours post ingestion, then a second level in 3-4 hours later. At normal levels, half-life is 1-3 hours. Half-lives exceeding 4 hours are consistent with hepatic necrosis (6). Toxic levels require monitoring of the liver function with AST (SGOT), ALT (SGPT), and bilirubin, in addition with study of glucose, creatinine, prothrombin time. Hepatic toxicity may appear 3-5 days after ingestion of a toxic dose (7). Time intervals between drug ingestion and hospital admission of patients presumed as latency period (8).

This study was approved by the Ethics Committee at Tabriz University of Medical Sciences and Health Services. Informed consents were obtained prior to entering into this study. Descriptive statistics were performed and we used the independent t-test for comparison of studied groups. Significant statistics had $p<0.05$ in order to receive a power of 90% confidence interval.

Results

There were 85 cases of acute acetaminophen poisoning during the study period (about 29% of patients with drug poisoning were admitted to our center). Females constituted 55 of cases (64%) versus 30 males (36%), giving a gender ratio of 1.8: 1. The majority of patients (68%) were between 16-30 and minority below 15 years of age (3.5%) (Table 1).

Table 1. Demographic features of patients with acetaminophen poisoning (N=85)

	Variable	N (%)
Age (years)	0-15	3(3.5)
	16-30	58(68)
	31-45	12(14)
	46-60	6(7)
	>60	6(7)
Gender	Female	55(64)
	Male	30(36)
Ingested dose (gr)	<5	17(20)
	5-10	10(11)
	11-15	27(32)
	>15	31(37)

In 76 cases (89%), the drug was ingested for attempted suicide and 9 cases (11%) were poisoned accidentally. Acetaminophen was implicated alone in all patients. The mean latency time was found to be 12 hours (range 1 to 36 hours). Data reveled that there is a close relationship between the latency period and duration of hospitalization ($p<0.05$) (Table 2).

Table 2. Relationship between latency period and hospital stay

Latency Period (hour)	Hospital Stay (hour)
<12	32.2*
>12	94.3

N=85 , * t-test $p<0.05$

Tablet was the predominant (100%) ingested form. It was apparent that 31 patients (37%) ingested more than 15 gr. A large proportion (72%) ingested more than 150 mg/kg, and 28% administered less than 150mg/kg.

All patients who came or were referred to the Sina Hospital for acetaminophen poisoning were initially managed at the accident and emergency department, prior to being admitted to toxicology ward. Initial recommended management includes gastric lavage, which was performed in all patients (9). In nine of them, it had been performed at another location before being referred to this hospital.

Activated charcoal was given to all patients while they were in the toxicology ward (10).

Using 150 mg/kg as the cut-off dose, 28% of patients had not ingested hepatotoxic doses (11). During their hospitalization course, 25 patients (29%) were asymptomatic and 75% had some form of symptoms which are listed in Table 3.

Table 3. Presented symptoms

Symptoms \ Dose	<150 mg/kg	≥150 mg/kg	p-value
Nausea	35	61	<0.001
Vomiting	25	58	<0.05
Excessive sweating	12	37	<0.05
Pale skin	11	29	<0.05
Anorexia	27	68	<0.001
Vomiting	19	49	<0.05
Malaise	39	47	<0.001
Abdominal pain	15	59	<0.05
Jaundice	6	61	<0.05
Confusion, stupor	2	12	<0.001

Interestingly, no patient died due to acetaminophen poisoning. Oral N-acetylcysteine (NAC) is recommended for these patients (7), therefore, it was given in 71 cases (83.5%). We had no serious complication due to NAC use, thus, therapy was continued. This side effect was reported as mild itching (12).

The mean time of hospital stay was 56.3 hours (range 12 to 240 hours). Patients who ingested a higher acute dose (>150 mg/kg) had a significantly longer duration of hospitalization (Table 4).

Table 4. Relationship between ingested dose and duration of hospitalization

Dose	Mean Duration of Hospitalization(hours)
>150 mg/kg (possible hepatotoxic)	71.8*
<150 mg/kg (unlikely hepatotoxic)	36.0

* N=85, t-test, p<0.05

Discussion

Acetaminophen is one of the most commonly used agents in our poisoned patients. After tricyclic anti-depressants, this drug is considered as the second step for self-poisoning. This resembles the poisoning picture reported from other centers (13,14). Similar to data reported from other countries this form of poisoning is more common among females (15).

According to our findings, majority of acetaminophen poisonings were due to suicidal attempts rather than accidental ingestion. The number of accidental self-poisonings and suicidal attempts has grown in recent years (16). This may be due to this fact that acetaminophen is an over-the-counter drug and also, is easily available in our region. In the UK, sales of over-the-counter acetaminophen are restricted to packs of 32 tablets in pharmacies, and 16 tablets in non-pharmacy outlets (15). Up to 100 tablets may be sold in a single transaction. In Ireland, the limits are 24 and 12 tablets, respectively (8). Following these regulations, there was a decline in the severity but not frequency of paracetamol poisoning cases reported to Guy's and St Thomas' Poisons Unit (15). It is unclear whether the decline in severity was a direct consequence of the regulations (15). Morgan et al. examined the change in deaths attributed to acetaminophen poisoning in England and Wales in the six years before and after a legislated reduction in the maximum pack size. Interrupted time-series analysis of regulations was used to reduce paracetamol (acetaminophen) poisoning (17). They did show statistically significant changes in deaths were attributed to acetaminophen poisoning after the regulations, but reported they found little evidence to suggest regulations caused the reduction (18). However, in Iran, one can buy hundreds of this drug without any limitation.

The biological outcome of acetaminophen poisoning depends on several factors. Chronic excessive alcohol consumption can induce CYP2E1; therefore, it increases the potential toxicity of acetaminophen (19). For this reason, analgesics such as aspirin or ibuprofen are often recommended over acetaminophen for relief of hangovers when other factors, such as gastric irritation, are not involved. Fasting is a risk factor, possibly because of depletion of hepatic glutathione reserves (20). Because of the wide availability of acetaminophen, there is potential for overdose and toxicity (9). Without timely treatment, overdose can lead to liver failure and death within a few days; acetaminophen toxicity is, by far, the most common cause of acute liver failure in both the United States and United Kingdom (21). It is sometimes used in suicidal behavior by

those who are unaware of prolonged time course and high mortality (likelihood of significant illness) is associated with acetaminophen-induced toxicity in survivors (5).

It is well documented that concomitant use of the CYP2E1 inducer isoniazid increases the risk of hepatotaxicity, though whether 2E1 induction is related to the hepatotoxicity in this case is unclear (22). Concomitant use of other drugs which induce CYP enzymes such as antiepileptic (including carbamazepine, phenytoin and barbiturates) have also been reported as risk factors (23). For this reason, we selected patients without these predisposing factors. In several studies, this selection is not performed, thus, greater mortality or morbidity may be seen due to this subject (19,21). The prognosis of acetaminophen toxicity varies depending on the dose and the appropriate treatment (19). In some cases, massive hepatic necrosis leads to severe hepatic failure with complications of bleeding, hypoglycemia, renal failure, hepatic encephalopathy, cerebral edema, sepsis, multiple organ failure, and death within days (24). In many cases, hepatic necrosis will run its course, but hepatic function may return and the patient may survive with liver function returning to normal in a few weeks (25). In Western countries, rate of deaths due to acetaminophen poisoning is high (3). It was the largest single cause of death from acute poisoning in a hospital in the UK (4).

In adults, single doses above 10 grams or 150 mg/kg have a reasonable likelihood of causing toxicity (11). Therefore, life threatening hepatic complications usually follows ingestion of more than 15g or blood level greater than 150mg/kg (11).Our study showed that 72% of our patients ingested more than this amount, which is lower than the findings reported in the UK (89%) (4). This finding may explain the higher rates of deaths and hepatotoxicity found in other studies (13,14). Some studies do not take into consideration the dose of ingested acetaminophen due to several reasons. Accurate dose estimations may not be determined accurately in the accidental group because many of these patients had an inadvertent ingestion of acetaminophen over several days, and also, a substantial number of patients in the suicidal group - whom are drowsy and sedated- cannot give an accurate history regarding the dose of acetaminophen ingested (26). Another important factor implicated to hepatotoxicity may be alcohol consumption, which is not usual in our country. The high rate of alcohol-related diagnoses in one cohort study reported by Saitz and colleagues, presumably contributed to this risk (27).

The majority of our patients were initially managed by gastric lavage and activated charcoal. These procedures might have contributed to the favorable outcomes in our setting. Both gastric lavage and activated charcoal can help to significantly reduce serum acetaminophen concentrations (10). The mean time from exposure to treatment has been reported to significantly affect the prognosis and final outcome of acetaminophen toxicity (4). Those with liver damage tend to seek treatment late in the hospital and consequently are given NAC after a longer delay (12). In this study, the majority of patients were presented within 9 hours after ingestion. The timely administration of NAC to these patients might have resulted in the favorable clinical outcomes generally seen in our patients.

Our study found that more than 83.5% of patients received NAC, although 37% ingested >15 g of acetaminophen. Therefore, it is possible that patients who were classified as "unlikely to be hepatotoxic" were also given NAC. This issue probably needs to be addressed in order to ensure the cost-effective use of NAC as well as to keep patients from any unnecessary exposure to the antidote (12).

Approximately 72% of our patients ingested more than 150 mg/kg. Data on the clinical course, however, showed that only 29% of patients were either asymptomatic or experienced some form of gastrointestinal distresses (71%). This shows the lower percentage of patients is predicted to be hepatotoxic. It was also revealed that both the higher dose group (>150 mg/kg) and the potentially hepatotoxic group had significantly a longer duration of hospital stay. This confirms that ingested dose is consistent with the expected duration of hospitalization.

According to these results, acetaminophen

poisoning is more likely to occur for suicidal attempt. However, the outcomes are more favorable than reported elsewhere (3). In fact, none of our patients in the suicidal group died or had to be referred for liver transplantation. It seems that most of them had suicidal thoughts and behavior, rather than actual attempts to end their life.

Furthermore, this study reveals that the clinical courses of patients are more compatible with prediction of toxicity based on reported ingested dose.

However, we recommend restricting the quantity of drug available for an over-the-counter medication, as the most pragmatic means of reducing acetaminophen-related suicide and liver failure.

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