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Original Article

Puzzling Situation of Acetaminophen Toxicity in a Referral Hospital, Tehran, Iran

Abdolkarim Pajoumand [a], Tahereh Alinia[b], Arezoo Mahdavinejad [a], Haleh Talaie [a*]

[a] *Toxicological Research Center, Department of Clinical Toxicology, Loghman-Hakim Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran.* [b] *Shahid Beheshti University of Medical Sciences, Tehran, Iran.*

Abstract

Acetaminophen carries a higher risk of overdose. A puzzling situation of acetaminophen toxicity was encouraging enough to explore the epidemiologic situation of acetaminophen toxicity and its outcomes among patients acquired poisoning. This cross-sectional study retrospectively reviewed the medical records of 185 patients with acetaminophen poisoning referred to Loghman Hakim Hospital. Toxicity determined by acetaminophen serum concentration and time elapsed after drug ingestion. Demographics, laboratory markers, toxic hepatitis, renal failures, and liver enzyme elevations were compared between toxic and non-toxic patients. Twelve cases belonged to the former group and 173 patients fitted with the latter one. Having a mean age of 24.27±7.19 and 21.58±3.47 years, respectively, females were predominant. The average serum acetaminophen level was 70.37±61.92 and 24.90±26.36 within toxic and nontoxic patients, respectively. Median of consumed tablets were estimated as 40 for non-toxic and 18 for toxic patients (p=0.017). Mean hospital stay was 1.75±1.05 days for toxic patients and 1.35±3.25 days for the non-toxic group (p-value<0.001), and of whom 92.4 % were discharged within the first day. The laboratory assessments revealed no significant difference between groups. No death was recorded. Whereas hepatotoxicity was present in three toxic patients, renal failure was predominant in non-toxic patients. Rarely, a rise in liver enzyme was noticed; however, 33.33 % of toxic and 2.31 % of the non-toxic group had elevated AST; and 33.33 % of toxic versus 1.73 % percent of non-toxic patients had increased ALT. Acetaminophen toxicity is a worldwide noteworthy cause of poisoning which has distinct mortality and morbidity rates and showed an amazing and undebatable poisoning effect in the present study. A comprehensive study is required to examine the possible reasons for the difference between Iranian acetaminophen products with other non-Iranian company products.

Keywords: Acetaminophen; Hepatotoxicity; Poisoning; Renal failure; Toxicity

Corresponding Author: Haleh Talaie, Toxicological Research Center, Department of Clinical Toxicology, Loghman-Hakim Hospital, Shahid Beheshti University of .Medical Sciences, Tehran, Iran
Tel: +982155418175
E-Mail: talaie@sbmu.ac.ir
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1. Introduction

Acetaminophen is one of the most common drugs. The popularity of acetaminophen has been increased because it is allegedly safer than aspirin. The availability of this product might be attributed to prevalence, low price, and effectiveness in pain relief.

Acetaminophen accessibility along with its ability to cause high toxicity made it have a much higher potential to cause an overdose. Acetaminophen toxicity is one of universal causes of poisoning [1]. The maximum safe daily dosage should not be greater than 4 g in a 24-hour period [2]. Excessive amount usage of this remedy can cause severe kidney, liver, and hepatorenal injuries [3]. It is well documented that a single dose ingestion of more than 10 to 15 g of this drug can cause severe or fatal liver injury secondary to massive hepatic necrosis [2].

There are non-specific early features of acute overdoses which are observed among those having acute toxicities, such as lack of coma, delay in onset of jaundice, and rapid fall in detectable acetaminophen plasma levels [4].

During 1989 to 1990s, an estimated 41, 200 cases of acetaminophen poisoning took place in England and Wales having a mortality of 0.40 %. Moreover, it is estimated that 150-200 deaths and 15-20 liver transplants occur as a ramification of poisoning each year in such regions [5]. A conducted study in Iran revealed that 11.4 % of drug-induced poisonings were due to acetaminophen ingestion [6]. Previous research in our country has indicated that the majority of cases consumed the hepatotoxic dosage, yet clinical courses were mild. Rarely, acetaminophen poisoning was associated with outcome [7]. Findings of another research indicate the normal level of enzymes presented in almost half of patients [8].

Acetaminophen has been widely used in Iran. Despite various international reports of acetaminophen toxicity, we experienced a different puzzling situation in our study. Therefore, the present research aimed to provide a perception of the current epidemiological situation of acetaminophen toxicity, clinical feature, toxic hepatitis varying degree, laboratory marker, and the clinical outcome among patients who intentionally acquired acetaminophen poisoning.

2. Materials and Methods

This retrospective cross-sectional study was performed from September 2013 to 2014. We collected data from intoxicated patients admitted straight forward from toxicological emergency room to the toxicological intensive care unit of Loghman Hakim Hospital Poison Center (LHHPC). This hospital is a unique care, teaching, and referral poison center in Tehran with nearly an annual average of 20,000 hospital visits. Our study was approved by the ethic committee of Shahid

Beheshti University of Medical Sciences (Research Project Number: 163.14.10.1393). The study complied with the guidelines of the Declaration of Helsinki. The patient's data maintain confidentially.

The patients were excluded from this study if they had the following attributes: (a) major systemic co morbidities, such as heart, lung, renal, or liver disease, (b) concurrent poisoning with other drugs, (c) cancer.

A trained nurse was responsible to extract basic, clinical, and laboratory data from the records of eligible patients. Individual baseline information consisted of age, gender, serum acetaminophen level ($\mu g\ mL^{-1}$), acetaminophen amount (consumed tablets, 500 mg per tablet), time elapsed between acetaminophen ingestion and hospital arrival (hour), length of hospital stay (days), acetaminophen type (simple or codeine), ICU admission, and history of underlying disease. The underlying diseases included hypothyroidism, cardiovascular accidents (CVA), Mitral Valve Prolapse (MVP), hyperlipidemia, and depressive disorder. Clinical manifestations incorporated the patient outcome which was defined as recovery, self-informed discharge, Vegetative, toxic hepatitis, and renal failure. Laboratory biomarkers were analyzed using Mindray auto-analysis.

The plasma acetaminophen level was measured by fluorescence polarization immunoassay. To detect toxicity total serum concentration of acetaminophen is considered to be proportional to the time elapsed since ingestion(4). This allows clinicians to timely manage the acetaminophen overdose. According to acetaminophen plasma concentration nomogram, ≥150 microgram/mL at four hours, ≥80 microgram/mL at four to eight hours, ≥40 microgram/mL at eight to 12 hours, ≥20 microgram/mL at 12 to 16 hours, ≥10 microgram/mL at 16 to 20 hours, ≥5 microgram/mL at 20 to 24 hours post ingestion indicates acetaminophen toxicity [9]. Acetaminophen associated toxic hepatitis is considered if the ALT level enhances above 1000 IU/L (10-12). Acute renal failure was defined as a serum creatinine level greater than 1.3 mg/dL(13). Also, enzyme elevation twofold than the normal value for Alanine transaminase (82 IU/L) and Aspartate transaminase (74 IU/L) was tested to track liver damages.

The continuous variables were described by means, standard deviations, and median; Laboratory data values presented as median. Categorical variables were expressed as numbers and relative frequency. Normality distribution and the equality of standard deviations were assessed before the analysis. Student t-tests and Man-Whitney tests applied for the continuous variables and Chi-square or Fisher tests used for categorical variables. We considered a p-value less than 0.05 to be significant. All analysis was performed using IBM SPSS Statistics version 20.

3. Results and Discussion

Records of 185 patients with intentional acetaminophen poisoning were examined. Of whom, 58 cases (31%) were male and 127 (69 %) subjects were female. The average (± SD)

age was 23.32 ± 68.7 for males and 24.45 ± 6.73 for females. It is notable that we only found 12 toxic patients.

Table 1 outlines the baseline characteristics of patients with acetaminophen poisoning who were categorized according to toxicity status. There was no significant age difference between these two groups. The mean serum acetaminophen level was 70.37±61.92 for toxic and 24.90±26.36 for non-toxic patients which were not statistically significant. The median of consumed tablets were 40 for non-toxic and 18 for toxic patients (p=0.017). The average time elapsed between acetaminophen ingestion and hospital arrival appeared to be higher in the patients with acetaminophen toxicity (18.25±14.95 h) than those without toxicity (4.39±3.76). The difference achieved statistically significant (p=0.017). The mean days of hospital stay were 1.75±1.05 for the toxic group and 1.35±3.25 for non-toxic one (p-value<0.001). Most of the patients (92.4 %) in this study were under observation for only one day.

Codeine overdose was the most common attribute, both toxic and non-toxic patients (66.70 and 52 percent, respectively). Merely one non-toxic patient was referred into the ICU (Data was not shown). No toxic patient had a past history of the underlying disease, but 11 cases of non-toxic patients had the underlying disease (Table1).

As shown in table 2, the laboratory examinations revealed no remarkable difference between toxic and non-toxic patients. Moreover, the highest values of

Table 1. Baseline characteristics of patients with acetaminophen poisoning (N = 185).

Variables		Non-toxic patients (n= 173)				Toxic patients (n=12)				P value
	Total (n=185)	Min	Max	Mean ±SD	Median	Min	Max	Mean ±SD	Median	
Age (median age in year)	24.10±7.04	13	57	24.27±7.19	23	16	27	21.58±3.47	22	0.470
Serum acetaminophen level (µg mL^{-1})	27.84±28.64	0	141	24.90±26.36	12.90	0.60	177	70.37±61.92	62.15	۰.۲۱۰
Acetaminophen amount (tablet, 500 mg per tablet)	23.38±17.37	1.30	120	21.82±15.08	18	18	120	45.99±29.94	40	0.017
Time elapsed between acetaminophen ingestion and hospital arrival (h)	5.29±6.18	1	20	4.39±3.76	3	2	48	18.25±14.95	16.50	0.017
Length of hospital stay (day)	1.37±3.17	1	43	1.35±3.25	1	1	4	1.75±1.05	1	<0.001
	Total (n=185)	N(%)				N(%)				P value
Female (%)	127 (68.60)	121 (69.90)				6 (50)				0.197
Acetaminophen kind										
Simple	79 (42.7)	75 (43.40)				4 (33.30)				0.741
Codeine	98 (53)	90 (52)				8 (66.70)				
Both	8(4.30)	8 (46)				0				
Underlying disease	11 (5.90)	11 (6.40)				0				-
Hypothyroidism	2 (18.20)	2 (18.20)				0				
CVA	1 (9.10)	1 (9.10)				0				
MVP	1 (9.10)	1 (9.10)				0				
Hyperlipidemia	1 (9.10)	1 (9.10)				0				
Depressive disorder	4 (36.40)	4 (36.40)				0				
Multiple disease	2 (18.20)	2 (18.20)				0				

Table 2. Laboratory data of patients with acetaminophen poisoning (N = 185).

Variables	Total (n = 185)				Non-toxic patients (n= 173)				Toxic patients (n=12)		p-value
	Mean ±SD	Median	Min	Max	Mean ±SD	Median	Min	Max	Mean ±SD	Median	
Urea(mg dL^{-1})	25.29±7.07	24	10	49	25.19±7.10	24	13	38	26.75±6.70	26.50	0.654
Cr (mg dL^{-1})	0.95±0.19	0.90	0.20	1.90	0.95±0.19	0.90	0.10	1.30	0.92±0.31	0.95	0.654
AST (Unit L)	57.51±217.80	23	11	808	32.46±65.83	23	14	2472	418.75±757.32	27.50	0.538
ALT(Unit L)	56.65±232.80	16	9	707	26.64±63.01	16	10	2355	489±787.59	25	0.064
ALP(Unit L)	179.32±79.29	168	68	620	181.26±80.23	169	69	278	153±58.97	162.50	0.758
Direct bilirubin (mg dL^{-1})	0.36±1.45	0.20	0.10	19.70	0.35±1.49	0.20	0.10	2.10	0.57±0.61	0.35	0.143
Total bilirubin (mg dL^{-1})	0.94±1.58	0.60	0.10	19.70	0.93±1.63	0.60	0.30	2.10	1.09±0.58	0.95	0.272

serum creatinine concentration, urea, AST, ALT, ALP, direct, and total bilirubin were also similar.

At the end of the analysis, there was no adverse effect for toxic patients. 10 patients recovered and two had discharged with their own consent. Only three toxic patients developed toxic hepatitis and, fortunately, no death was recorded. Renal failure was found in one toxic and nine non-toxic patients. Totally rise in the liver enzymes was less prevalent in poisoned patients, however, the AST elevation relegated to the toxic group (33.33 percent versus 2.31% of non-toxic). ALT elevation was 33.33 percent among toxic and 1.73 among non-toxic patients.

The present research has been carried out among patients who referred to a unique care, teaching, and referral poison center in Tehran. This feature makes the sample representative of all poisoned patients in the city. This study demonstrated a high average level of serum acetaminophen level among poisoned patients. Regardless of this clinically important characteristic, there were only 12 toxic patients, of whom only three had hepatic toxicity.

Acetaminophen is a renowned anti analgesic pyretic agent. Its overdose results in toxic hepatitis or renal failures. It is documented that patients with toxic hepatitis had higher serum acetaminophen levels compared to patients without toxic hepatitis. Although, the serum acetaminophen level had not been recognized to be a considerable risk factor for toxic hepatitis complication after ingestion [2]. In the present study, hepatotoxicity recorded in 3 cases of the toxic group patients. Similar to Yi-Chou Hou *et al.* [2], the hepatotoxicity onset of patients were presented within the first hours after acetaminophen consumption. This was in contrary to the Paraquat poisoning which the symptoms of toxic hepatitis usually developed up to 6 days after subjection to the drug [2, 14].

The total serum acetaminophen level of toxic patients was significantly greater than the non-toxic group, which was much higher than the maximum recommended dose (4 g)

Table 3. Outcome of patients with acetaminophen poisoning (N = 185).

Variable	Total (n = 185)	Non-toxic patients (n= 173)	Toxic patients (n=12)
Made a recovery	178 (96.2۰)	168 (97.10)	10 (83.33)
Vegetative	1 (0.5۰)	1 (0.57)	0
Discharged with his consent	6 (3.2۰)	4 (2.80)	2 (20)
Developed toxic hepatitis	۳ (۱.۶۲)	0 (2.31)	3 (25)
Developed renal failure	10 (5.4۰)	9 (5.20)	1 (8.33)
AST elevation	8 (۴)	4 (2.31)	4 (33.33)
ALT elevation	7 (3.78)	3 (1.73)	4 (33.33)

pertaining to adult [2]. It was really distinctive in the present research that there was not any reliability between the documented self-reported acetaminophen levels and the laboratory measured dose. It was likely that patients wanted to exaggerate the number of ingested tablets because of attention deficit or suicidal attempt.

In one study, a patient died of liver failure as a result of toxic hepatitis, and the overall mortality rate was estimated as 0.5 %. In the current study no mortality has been recorded, but the length of hospital stay in the majority of patients was just one day [2]. In mortality rate report from the US that acetaminophen-related acute hepatitis and liver failure was around 19–30 % [15, 16]. Another confirmatory document by Larson et al. reported that 27 % of the American patients with acute liver failure died within 3 weeks [17].

Oral N-Acetyl cysteine (NAC) properly has avoided hepatotoxicity, regardless of the initial serum acetaminophen level and if it was started within eight hours of the ingestion, but did not depend on whether it was started 0-4 or 4-8 hours after ingestion [18]. The approved FDA dosage regimen for oral NAC starts with a loading dose of 140 mg/kg, to be offered every 4 hours [19]. The treatment course duration is 72 hours [19]. All the patients in our study had received the NAC antidote even after 36 hours of acetaminophen ingestion. As Chan stated the time passed between acetaminophen ingestion and treatment is the key prognostic factor for liver toxicity, just 50 % of patients in his study got the NAC antidote appropriately and late presentation (23 %) was the main reason for continuing morbidity [20]. A study by Hou *et al*., in Taiwan reported 78.6 % of patients received NAC properly and the elapsed time between acetaminophen ingestion and hospital arrival was 6.2 ± 6.0 hours and resulted in one death (2). It is still obscure whether the variability of NAC antidote use could possibly affect the prediction of time elapses for toxic hepatitis.

There were rare renal failure occurrence secondary to acetaminophen poisoning, approximately 1-2 %. Renal involvement can occasionally occur without prior liver disease, and early renal manifestations frequently arise

in the second day after the acute acetaminophen poisoning up to a seventh day [21]. However, in the present research, there were 10 cases (5.4 %) of developed renal failure on the first day and none of them had prior hepatotoxicity. Also, nine cases of renal failure were in the non-toxic group. Based on Waring WS and Jones Al studies, maximal renal damage lacks beyond the peak liver injury and recovery is also more protracted, his data are in accordance with the present study [22, 23]. According to the rhabdomyolysis definition by CPK greater than five times of normal (≥975 IU/L), in the current study, no cases fit this category on admission day. It is compatible with our previous study, which the most common cause of rhabdomyolysis was opium and acetaminophen was not recorded [24]. The majority cases of this study were females similar to previous studies [25, 26]. This may be a direct result of higher clearance involving acetaminophen due to increased activity of the glucuronidation pathway that comes about mostly by UDP-glucuronosyl transferases (UGT) in males than females [27]. In the current study, less than 10 patients had raised hepatic enzymes. Moreover, there was no statistical significance between toxic and non-toxic patients.

4. Conclusion

We have to additionally point out some constraints in our investigation. Due to higher turnover among patients with poisoning ward, acute and severe toxicity, and short term hospitalization, there is the possibility of incompleteness within the patient profile and data missing. There seemed to be an inconsistency between the acetaminophen level measured by laboratory and stated dose by patients. This can be because of patient exaggeration about taking a dose or maybe a laboratory error. Acetaminophen overdose, which has proved toxicity effect with defined mortality and morbidity, showed an amazing undebatable poisoning effect in the present study. A comprehensive study is required to examine the possible reasons for the difference between Iranian acetaminophen products with other non-Iranian company products.

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