

Original Article

Acetaminophen Serum Levels in Patients with unknown Poisoning and Loss of Consciousness

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ABSTRACT

Background: The aim of this study was to evaluate the serum levels of acetaminophen in patients with unknown poisoning and loss of consciousness, and to assess whether measuring serum acetaminophen level in all patients with drug overdose or decreased level of consciousness changes outcome. **Methods & Materials:** In a descriptive-analytical study, 300 patients with loss of consciousness and a history of drug toxicity with an unknown drug that referred to the emergency unit constituted the study sample. Serum acetaminophen levels of patients, the outcome, mortality, and morbidity of patients were evaluated. **Results:** The mean age of patients was 28.88±8.67 years. The minimum age of patients was 15 years and the maximum age of patients was 58 years. The mean serum level of acetaminophen in patients was 0.62±0.55 µg/ml. The highest level and the lowest level of acetaminophen in patients were 2.8 µg/ml and 0.2 µg/ml respectively. Serum acetaminophen level in patients was less than the toxic level (less than 30 µg/ml). **Conclusion:** Based on the findings of this study, acetaminophen as a widely used and available drug is not a common cause of poisoning in patients with loss of consciousness in our region.

INTRODUCTION

The use of acetaminophen (also known as paracetamol or APAP) as an analgesic and antipyretic has expanded in the past decades. One important reason for its widespread use can be related to the lack of gastrointestinal toxicity in comparison with non-steroidal anti-inflammatory medications (1,2). Acetaminophen overdose is a common problem nowadays. We should also highlight that people use acetaminophen to commit suicide (3,4). Acetaminophen poisoning is a common cause of poisoning in America and it is one of the leading causes of mortality and morbidity due to poisoning. We should accentuate that up to 48% of all poisoning admissions to hospitals and approximately 300 deaths per year in UK are the causes of acetaminophen poisoning (5).

In therapeutic doses, acetaminophen is a safe drug and has the U.S. Food and Drug Administration (FDA) pregnancy risk factor rating of B, and no well-controlled studies demonstrate a risk of acetaminophen use to the fetus in any

trimester (6,7), although some recent studies suggest that acetaminophen can impair maternal, fetal, and long term children's health. These studies recommended that further investigations are needed (8,9). Currently, in children and pregnant women and also during breast-feeding, acetaminophen is considered as a safe drug and it is the first choice of physicians for analgesic or antipyretic effects (10,11).

Acetaminophen can also be combined with other pharmaceutical compounds for the treatment of various symptoms. This poisoning has not significant signs or symptoms in early phases. There are approximately 184 different types of medicinal compounds of acetaminophen as Over-The-Counter (OTC) in various dosage forms such as tablet, capsule, suppository, etc. (12).

The high prevalence of acetaminophen overdose, its complications, and mortality and morbidity can be regarded as a burden of cost for healthcare systems. Dose-dependent hepatotoxicity effects of acetaminophen, is one of the main

concerns of clinicians about acetaminophen overdose. Early diagnosis and treatment with N-acetylcysteine as an antidote of acetaminophen in early hours after digestion can decrease the mortality and morbidity of patients significantly (13-16).

As a result, diagnosis and treatment is based on history taking and acetaminophen serum level concentration. Because of severity complications after poisoning and the availability of effective antidote, many physicians take acetaminophen serum level samples in all patients without paying attention to history.

At emergency departments and trauma centers, all adult patients, after suspicion of drug use or decreased level of consciousness or confusion, are screened for acetaminophen and other co-poisoning on a regular basis.

This study was conducted due to the importance of acetaminophen overdose and the significance of its early diagnosis and treatment. The aim of this study was to evaluate the serum levels of acetaminophen, prognosis of patients with loss of consciousness, and patients with a history of unknown drug toxicity.

Patients and Methods

Study design

This descriptive-analytical study was conducted in a 2-year period from April 2013 to April 2015 in the emergency units of the educational medical centers of Tabriz University of Medical Sciences (these centers are referral centers for toxicology in the North West of Iran). We randomly selected patients using Rand list software (version 1.2) and (using Morgan Table with $\alpha=0.05$ and confidence level 95%) by 300 adult patients (over the age of 16 years) with serum acetaminophen level concentration, loss of consciousness and a history of drug toxicity with an unknown drug entered the study. A validated and standard form was designed in order to collect the following data: demographic information of patients, history of poisoning, arrival time to the emergency unit, quantity of poisoning, laboratory data, time of overdose, type of drug overdose, risk factor of acetaminophen poisoning, physical exam findings, vital sign, management of patients, and antidote administration. APACHE2 calculation for severity of disease, trauma, or comorbidity.

Inclusion criteria were loss of consciousness and a history of taking an unknown pharmaceutical agent by the patient or his/her entourage. Clarification of medication was considered as the exclusion criterion. On arrival to the emergency department, after hemodynamic stabilization. All patients received the standard N-acetylcysteine after emergency admission.

The demographic data of patients including age and sex were collected as well. Vital sign and other laboratory tests were performed. Serum acetaminophen levels of patients were measured and if they were in a therapeutic dose (10-25 mcg/ml) or higher they were measured again 4 hours later. The photometric method was used to determine serum acetaminophen levels. Outcome, mortality and morbidity of patients, and the length of hospitalization were evaluated.

Ethics

The Research Ethics Committee of Tabriz University of Medical sciences approved this study.

Statistic

SPSS software package version 21 for windows (SPSS Inc., IBM, Chicago, USA, 2012) was used for statistical analysis. Collected information is presented as mean±standard deviation (mean±SD) and as frequency and percentage. To compare quantitative variables, Student T-test was used and for qualitative variables, Chi-square and Fischer exact test were applied if needed. P-value less than 0.05 was considered as significant.

RESULTS

From April 2013 to April 2015, approximately 425 patients were observed in the emergency department. Of this, 125 patients were excluded (because of age lower than 16 years old, insufficient documentations and history of Paracetamol or Acetaminophen usage) and 300 patients entered the study (Figure 1).

115 (38.3%) patients were male and 185 (61.7%) patients were female. Male to female ratio was 1:1.60. The mean age of patients was 28.88±8.67 years, and mean ages of male and female were 31.22±9.00 and 27.43±8.15 respectively. The minimum age of patients in both male and female p.

Patients was 15 years old. Maximum ages of patients for male and female were 58 and 56 years respectively. The mean age of male patients was significantly higher than the mean age of female patients (P=0.001). Demographic characteristics, vital sign, invasive and severity of disease are shown in Table 1.

221 (73.7%) patients were lethargic when they first arrived to the emergency department, whereas 67 (22.3%) and 12 (4.0%) patients were obtundate and had a coma respectively. The level of consciousness in male and female patients was according to Table 2.

Table 1. Demographic characteristics, vital sign, invasive and severity of disease in 300 patients

Characteristics	Mean	P-Value
Age	28.88±8.67	0.66
WBC	11000±101	0.001
Creatinine	1.04±0.01	≤0.001
MAP	89.66±0.92	≤0.001
SBP	109±0.99	≤0.001
DBP	80±0.56	≤0.001
HR	112±14	≤0.001
RR	12±3	≤0.001
GCS	9±1	≤0.001
Hct	42.1±1.11	≤0.001
Hco3	20±2	≤0.001
Na	149±5.31	≤0.001
K	3.99±0.85	≤0.001
PaO ₂	59±8.41	≤0.001
APACH 2	18±1	≤0.001

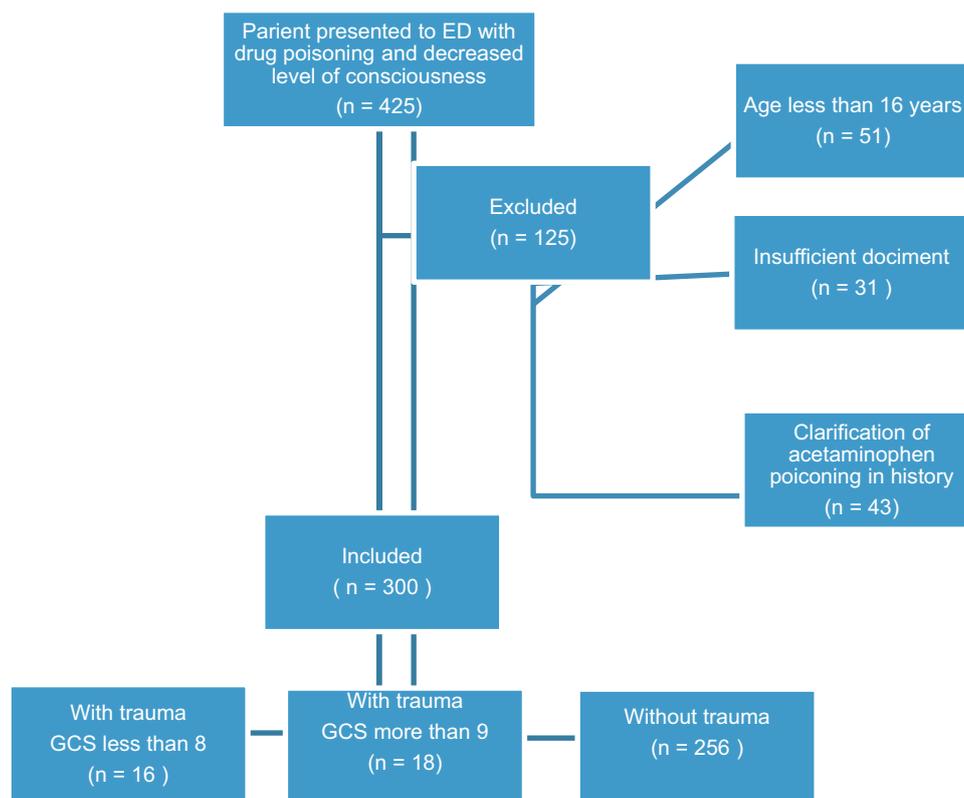


Figure 1. Patients selection chart

Comparing males and females in terms of the level of consciousness, the incidence of light coma in males was significantly higher than females ($P=0.028$).

Among patients, the most frequent serum level of co-poisoning with acetaminophen overdose was for opium, alcohol, and benzodiazepine at 61%, 60.7%, and 53.6% respectively (Table 3).

The mean serum level of acetaminophen in patients was 0.62 ± 0.55 mcg/ml. In addition, it was 0.56 ± 0.50 mcg/mL and 0.65 ± 0.57 mcg/ml in males and females respectively. The minimum serum level of acetaminophen in both groups was 0.2 mcg/ml. In addition, the maximum level of serum acetaminophen for both males and females was 2.4 mcg/mL and 2.8 mcg/mL respectively. There was no significant difference between male and female regarding the serum level of acetaminophen ($P=0.170$). The most serum acetaminophen level was seen between opium and benzodiazepine co-poisoning, it was 1.3 ± 0.32 mcg/L and 1.15 ± 0.59 mcg/L, respectively.

Because serum levels of acetaminophen in all patients was lower than the therapeutic dose (10-25 mcg/ml), serum levels of acetaminophen in patients were measured only one time.

Blood glucose levels of patients as a possible factor in the loss of consciousness were measured on arrival at the emergency department. The mean of blood glucose level was 101.89 ± 22.86 mg/dl and the minimum level of blood glucose in patients was 68 mg/dl. As the blood glucose levels of none of the patients were in a range that could cause the loss of consciousness, hypoglycemia was not considered as a cause for the loss of consciousness in the studied patients.

The mean length of hospitalization in patients was 4.43 ± 1.23 days. There was no mortality or any kind of mor-

Table 2. Level of consciousness in male and female patients

Patients Consciousness	Total	Male	Female
Lethargic	221 (73.7%)	81 (70.4%)	140 (75.6%)
Obtundation	67 (22.3%)	25 (21.7%)	42 (22.7%)
Comma	12 (4.0%)	9 (7.8%)	3 (1.6%)

bidity in patients and all patients discharged healthily after recovery. Only in 2 patients liver amino transferases were increased partially at the time of admission (Table 4). This condition became normal during hospitalization and no evidence of sustained liver damage was observed.

DISCUSSION

Acetaminophen as a non-opioid, analgesic, and antipyretic safe medication is widely used all over the world for pain relief by all age groups (17,18,19). It is available by prescription and OTC and also exists in a combination form with other drugs (20).

Not only acetaminophen overdose is a relatively common problem that may cause severe complications, but also due to its non-specific symptoms like nausea, vomiting, tiredness, confusion, and coma, it is important to diagnose acetaminophen overdoses immediately in emergency centers (21,22).

Studies suggest measuring serum acetaminophen and serum APAP-protein adducts to identify acetaminophen toxicity. This may be useful for cases that lack historical data or other clinical information. With the early treatment of

Table 3. The frequencies of the most common causes of co-poisoning

Cause	Number (%) of patients
Alcohol intoxication	123 (41)
Drug co-poisoning	
Salicylate	30 (10)
Tricyclic antidepressant	72 (24)
NSAIDS	9 (3)
Beta blocker	6 (2)
Opium	96 (32)
Banzodiaephine	105 (35)
Other	19 (7)
Seizure	60 (20)
Traumatic Brain Injury (unknown mechanism)	30 (10)
Infection	33 (11)
Arthritis	15 (5)
Pyelonephritis	

Table 4. The liver function test and coagulation profile test

	Admission	After 4 ^h	After 24 ^h	P-value
AST	38±3	37±3	37±2	≤0.002
ALT	36±2	36±3	36±4	≤0.002
PT	13±1	13.2±2	12±1	≤0.002
INR	2±0.1	2±0.2	2±0.15	≤0.002

acetaminophen overdose, physicians can prevent its severe complications (23,24). If some people suffer from acetaminophen toxicity even at therapeutic doses (< 4 g/day), then acetaminophen uses should be considered as a possible contributing factor in patients with suspected symptoms (25).

This study was conducted to evaluate the serum level of acetaminophen in patients with unknown poisoning who referred to our emergency centers with loss of consciousness. Hypoglycemia was not found in any patients, so hypoglycemia as a common cause for the loss of consciousness was ruled out in patients. All patients had a history of unknown drug consumption. Acetaminophen serum levels as a widely used and available pharmaceutical agent were measured in patients.

In the present study, serum levels of acetaminophen were lower than the toxic level and even lower than the therapeutic dose (10-25 mcg/ml) in all patients and the maximum level of serum acetaminophen in patients was 2.8 mcg/ml. As a result, acetaminophen toxicity was not detected in our study. In this study no mortality or morbidity were seen and all patients recovered without complications.

In a Canadian population-based epidemiologic study regarding the emergency department visits for acetaminophen overdose, 2699 patients were studied. The incidence of acetaminophen overdose was approximately 46 per 100 000 population. This study proposed that some subgroups of patients like young females were at a greater risk and educational

and preventive operations may be practical in this area (26). In a similar study in the United States, the incidence of acetaminophen overdose was estimated approximately 20 per 100 000 population (27).

Finally, although in our study acetaminophen overdose was not demonstrated, several recent review studies suggested acetaminophen overdoses as a common issue that can cause acute liver damage. Thus, it is necessary to pay heed to this damage in all over the world (28-30). We propose similar studies to be conducted in other centers and emergency centers must be aware of acetaminophen overdoses in their cares.

Limitation

Our study was done in one center and the number of patients are few; it is better to run this study in multicenter base with higher number of patients; then we can strongly report our findings.

CONCLUSION

Based on the findings of this study, acetaminophen as a widely used and available drug is not a common cause of poisoning in patients with loss of consciousness in our region. Studies with a sufficiently large sample size are necessary to be done.

ETHICS COMMITTEE APPROVAL

Ethics committee approval was received for this study from the ethics committee of regional ethic committee of Tabriz University of medical sciences (date/no:92/3-8/26).

INFORMED CONSENT

Written informed consent was obtained from patients or relatives.

PEER-REVIEW

Externally peer-reviewed.

AUTHOR CONTRIBUTIONS

Concept -A.A., S.S.V; Design -S.M; Data Collection and/or Processing G.B.R, P.H, Analysis and/or Interpretation – S.S.V., S.T; Literature Review -P.H.; Writing -S.T; Critical Review – A.A.

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