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Research Paper

Hepatotoxicity Among Poisoned Patients: A Cross-sectional Study

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ABSTRACT

Background: Drug-induced liver injury is a major cause of hepatitis worldwide. In patients diagnosed with acute poisoning, drug-induced liver injury is a critical challenge. This study aims to evaluate the pattern of hepatotoxicity in poisoned patients admitted to Loghman Hakim Hospital.

Methods: In this cross-sectional study that was conducted at Loghman Hakim hospital, the clinical records of poisoned patients were evaluated and patients with hepatotoxicity were selected for final analysis. The clinical and para-clinical information of these patients was recorded. The SPSS software, version 23. was used for statistical analysis.

Results: A total of 260 cases were included in this study. The Mean±SD age of patients was 38.24±16.29 years and most of them were male (79.2%). Patients with narcotics poisoning had the highest prevalence (38.5%), especially when they were taken together with acetaminophen or benzodiazepine. In addition, among the patients studied, those with underlying cardiovascular disease are more likely to develop hepatotoxicity.

Conclusion: In conclusion, among people with various types of poisoning, it seems that narcotics (opium, heroin, methadone, etc.), particularly when taken together with acetaminophen or benzodiazepines, cause hepatotoxicity and increase serum levels of liver aminotransferases. Also, in the study population, patients with underlying cardiovascular disease had a higher chance of liver injury. Therefore, clinicians are recommended to accurately monitor the sign and symptoms of hepatotoxicity in these populations.

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1. Introduction

Drug-induced liver injury is one of the main causes of liver damage. The risk of drug-induced liver injury differs significantly based on the consumed drug. In the United States and Europe, antimicrobial agents are the main culprit, for example, amoxicillin/clavulanate, while in Asians, dietary and herbal supplements are the major cause of drug-induced liver injury [1-3]. Toxicity and poisoning can cause liver injury. Hepatotoxicity usually occurs a few hours after poisoning, which is generally followed by damage to other major organs. The clinical phenotype of drug-induced hepatotoxicity is usually hepatic necrosis. Initially, serum aminotransferase and lactate dehydrogenase (LDH) levels increase significantly with increasing alkaline phosphatase. Necrosis and fat changes can be detected in histopathology [4]. Previous research has been conducted on various pharmaceutical agents and substances that are abused and ultimately cause liver damage. Some substances have received more attention for causing liver injury, including cocaine, amphetamine, oxycodone, heroin, nicotine, cannabis, marijuana, fentanyl, meperidine, methadone, hydromorphone, and chemotherapy agents [5]. Paracetamol is also known for its hepatotoxicity in cases of poisoning. More than 300 000 hospitalizations in the United States per year and more than 42% of all cases of acute liver failure are due to acetaminophen overdose. In addition, the incidence of liver failure due to acetaminophen has increased since 1990 [6]. Taking acetaminophen with opioids as a fixed combination drug has been reported to result in a specific type of liver injury [7]. Up to yet, no comprehensive observational study has been conducted to evaluate the pattern of hepatotoxicity in poisoning cases. This study aims to evaluate the pattern of hepatotoxicity in poisoning cases admitted to our hospital.

2. Materials and Methods

Study patients

The present study was a cross-sectional study conducted between 2018 and 2019. The study population included all patients who were admitted to Loghman Hakim Hospital in Tehran City, Iran, with the diagnosis of acute drug poisoning. The Ethics Committee of Shahid Beheshti University of Medical Sciences (SBMU) approved the design of the study (number: IR.SBMU.RETECH.REC.1398.098). Patients' clinical records were reviewed retrospectively and the files with incomplete information entry or inaccurate registration were excluded from the study. Besides, only patients whose serum levels of liver aminotransferases were four times normal or patients whose serum levels of liver aminotransferases were more than 1000 U/L were included in the study. Therefore, 260 files in which the registered information was complete and met the study entry criteria were included in the study. In all stages of the study, patient information was kept confidential.

A researcher-made checklist was used to collect the data, which consisted of two general sections. The first section included demographic information, such as age, sex, underlying disease, type of poisoning, hospitalization and intensive care unit (ICU) duration, and outcome. The second part included some laboratory parameters, such as levels of liver aminotransferases, prothrombin time (PT), partial thromboplastin time (PTT), international normalized ratio (INR), albumin, and bilirubin. Finally, the extracted data were imported into SPSS software v. 23 (IBM, USA). Frequency (percentage) for the nominal variable, Mean±SD for the numeric variable with normal distribution, and median (interquartile) for the numeric variable with non-normal distribution were used to report descriptive statistics. The categorical variables were compared using the χ^2 test. $P<0.05$ was considered significant.

3. Results

In this cross-sectional study, 260 cases were reviewed. These cases were admitted to Loghman Hakim hospital with the diagnosis of acute poisoning while experiencing hepatotoxicity during the hospitalization time. The Mean±SD age of patients was 38.24±16.29 years. Most of the patients were male (206; 79.23%). The median time from ingestion to admission was 12 hours. Cardiovascular diseases were the most common underlining condition of patients (17; 6.54%). Among patients who suffered from two or more underlying diseases, 9 cases had cardiovascular, 4 cases had diabetes, 3 cases had an endocrine disease, 2 cases had renal failure, 2 cases had pulmonary disease, one case had hepatitis, one case had coagulopathy, and one case had rheumatoid arthritis (Table 1).

In patients with serum levels of liver aminotransferases four times normal, 38.5% had narcotics (opium, heroin, etc.) overdose, 5.4% had alcohol overdose, 5.0% had acetaminophen ingestion, and 4.6% had benzodiazepine (BZD) ingestion. These cases were the most frequent types of intoxication in the study population. In patients with multi-drug intoxication (90;

Table 1. Demographic characteristics and laboratory parameters of patients

Characteristics	Variables	No. (%)/Mean±SD
		Statistics
Age	Mean±SD	38.2±16.3
Gender	Male	206(79.2)
	Female	54(20.8)
Underlying disease	Endocrine disease	2(0.8)
	Renal failure	3(1.2)
	Hepatitis	3(1.2)
	Cardiovascular disease	8(3.1)
	Pulmonary disease	6(2.3)
	Seizure	7(2.7)
	Diabetes mellitus	4(1.5)
	Hematological disease	1(0.4)
	Two or more of above disease	15(5.7)
	Others	11(4.2)
	No underlying disease	200(76.9)
	ALT (U/L), median (IQR25-IQR75)	299(170-646)
	AST (U/L), median (IQR25-IQR75)	363(237.5-676.5)
	ALP (U/L), median (IQR25-IQR75)	239.5(182-308)
	Bilirubin total (mg/dL), median (IQR25-IQR75)	1.3(0.8-2.1)
	Bilirubin direct (mg/dL), median (IQR25-IQR75)	0.5(0.3-0.8)
	Albumin (g/L), median (IQR25-IQR75)	3.8(3.3-4.2)
	PT (s), median (IQR25-IQR75)	16(14-21.8)
	PTT (s), median (IQR25-IQR75)	37.2(32.3-46)
	INR, median (IQR25-IQR75)	1.52(1.23-2.28)
	AST or ALT >1000 U/L, No.(%)	57(21.92)
	AST and ALT <1000 U/L, No.(%)	203(78.08)
	Hospitalization duration (d), Mean±SD	7.31±11.25
ICU admission	Yes	128(49.2)
	No	132(50.8)
	ICU duration (d), Mean±SD	5.32±10.32
Outcome	Discharged	196(75.4)
	Died	64(24.6)

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PT: prothrombin time; PTT: partial thromboplastin time; INR: international normalized ratio; ICU: intensive care unit; AST: aspartate transaminase; ALT: alanine transaminase; ALP: alkaline phosphatase; IQR: interquartile range.

Table 2. Type of poisoning in patients who developed hepatotoxicity

Patients with Quadrupled Liver Aminotransferases		Patients with AST or ALT Levels >1000 U/L	
Type of Poisoning	No. (%) Values	Type of Poisoning	No. (%) Values
Ferrous sulfate	1(0.4)	Ferrous sulfate	1(1.7)
ALP	8(3.1)	ALP	-
CO	3(1.2)	CO	-
Narcotics	100(38.5)	Narcotics	24(42)
Stimulants	2(0.8)	Stimulants	2(3.5)
Pesticides	10(3.8)	Pesticides	2(3.5)
Alcohol	14(5.4)	Alcohol	-
BZD	12(4.6)	BZD	4(7)
TCA	3(1.2)	TCA	-
Acetaminophen	13(5)	Acetaminophen	3(5.3)
Anxiolytic	1(0.4)	Anxiolytic	-
Cardiovascular medications	1(0.4)	Cardiovascular medications	-
Gastrointestinal medications	1(0.4)	Gastrointestinal medications	-
MDT	90(34.6)	MDT	21(36.8)
Unknown toxicity	1(0.4)	Unknown toxicity	1(1.7)
Total	260(100)	Total	57(100)

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BZD: Benzodiazepines; ALP: alkaline phosphatase; TCA: tricyclic antidepressant; MDT: multidisciplinary teams; CO: carbon monoxide; AST: aspartate transaminase; ALT: alanine transaminase.

34.6%), 37 (14.2%) cases had taken both narcotics and benzodiazepines (BZD) and 13 (5.0%) cases had taken both narcotics and stimulants. In patients with serum levels of liver aminotransferases >1000 U/L, 42% had narcotics (opium, heroin, etc.) poisoning, 7.0% had benzodiazepine poisoning, and 5.3% had acetaminophen poisoning as the most frequent type of poisoning. In this group, patients with multi-drug intoxication have used methadone in 14 cases (24.6%) and BZD in 11 cases (19.3%) (Table 2).

The results of liver aminotransferases showed that the median (IQR25-IQR75) of alanine transaminase (ALT) was 299 (170-646) U/L. The aspartate transaminase (AST) also showed a significant increase of 363 (237.5-676.5) U/L. The alkaline phosphatase (ALP) also was reported as 239.5 (182-308) U/L. No significant increase in bilirubin was detected. The albumin level of patients was in the normal range and no significant coagulopathy was observed. Table 1 shows the laboratory results of patients.

The average duration of hospitalization in ICU in the study population was 7.31 and 5.32, respectively. Among the studied patients, 64 cases died, and the in-hospital fatality rate was higher among patients with serum levels of liver aminotransferases greater than 1000 U/L (33.3%) than among patients with serum levels of liver aminotransferases four times normal (22.2%), although this difference was not statistically significant (P=0.084).

4. Discussion

In patients with serum levels of liver aminotransferases four times normal and in 57 patients with ALT/AST above 1000, a high percentage of patients had metha-

done poisoning as a single drug or in combination with other substances. For instance, in patients with alanine transaminase/aspartate transaminase (ALT/AST) above 1000, 38.5% of patients were poisoned with opium, of which 8 patients had opium alone and the rest with other substances, such as acetaminophen or BZD. It is noteworthy that most patients with hepatotoxicity had multi-drug intoxication, mainly including narcotics and benzodiazepines.

While the main reason for liver injury in narcotics abusers, especially among persons who inject drugs is related to hepatitis B virus (HBV) and hepatitis C virus (HCV) infection, as well as alcohol (since most of those who use drugs also have a history of alcohol abuse), opioids may also have a direct contribution in liver injury. Many opioids, such as oxycodone, methadone, fentanyl, and tramadol are metabolized in the liver via the P450 system. UGT2B7 enzyme in the liver is involved in the glucuronidation of some opioids, including morphine, oxymorphone, and hydromorphone [8]. In addition to these metabolic pathways, lipid oxidation and mitochondrial oxidative injury may also result in liver injury initiation or progression [9, 10]. δ-opioid receptors contribute significantly to cellular development and are found in abundance within liver tissue, which can induce or exacerbate liver injury following an opioid overdose [11].

Histopathologic evaluation of hepatocytes taken from rat models of chronic opioid use has illustrated various kinds of histological anomalies in the liver [12]. The administration of morphine to rat hepatocytes was reported to increase cell death [13]. It was reported that chronic heroin abuse in humans elevates the level of liver aminotransferases and other biochemical markers particularly ALT, lactate dehydrogenase, and lipid peroxides which may suggest direct hepatotoxic effects sustained by these drug metabolites [14]. Postulated indirect mechanisms of liver injury due to narcotic abuse include derangement of cholesterol and bile acid metabolism and severe constipation, which may lead to increased intestinal permeability and bacterial translocation [15]. Moreover, in the present study, the population of men was 4 times more than women, which is probably due to the higher rate of narcotic abuse among men compared to women [16].

According to the data, cardiovascular diseases were the most common underlining condition of poisoned patients who developed a liver injury. It has been known for many years that the liver and the heart are closely related [17]. Therefore, acute and chronic heart failure can trigger liver injury in poisoned patients. Furthermore, studies showed that drug abuse and cardiovascular disease (CVD) are also closely related [18]. More research is needed to investigate the cause-effect relationship between these parameters.

The remarkable point of this study is the in-hospital fatality rate in the two groups of patients. Although patients with ALT or AST enzymes above 1000 U/L had a higher rate of in-hospital fatality (22.2% vs 33.3%) compared to patients with ALT or AST levels higher than four times the normal range, this difference was not statistically significant (P>0.05). Therefore, liver damage following an overdose seems not to be fatal, although a robust survival analysis would be decisive in this regard.

The major limitation of this study was the small sample size. This study was conducted on patients admitted to a single medical ward and by conducting a similar multicentered study, this limitation will be removed. Another limitation was incomplete medical records which forced us to discard some cases. Moreover, due to the disparity in the prevalence of different kinds of poisoning, subgroup analysis provides a better picture of hepatotoxicity among poisoned patients, which requires a large sample size.

5. Conclusion

In conclusion, among people with various types of poisoning, narcotics (opium, heroin, methadone, etc.) seem to cause hepatotoxicity and increased serum levels of liver aminotransferases, particularly when taken together with acetaminophen or benzodiazepines. Also, in the study population, patients with underlying cardiovascular disease had a higher chance of liver injury. Therefore, clinicians are recommended to accurately monitor the sign and symptoms of hepatotoxicity in these populations. Although the death rate in patients with ALT/AST levels four times normal was lower than in patients with AST/ALT levels above 1000 U/L (22.2% vs 33.3% respectively), no statistically significant difference was observed between the two groups in terms of survival.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the Ethics Committee of the Shahid Beheshti University of Medical Sciences (SBMU) (Code: IR.SBMU.RETECH.REC.1398.098).

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Authors' contributions

All authors equally contributed to preparing this article.

Conflict of interest

The authors declared no conflict of interest.

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