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Case Report: Effect of Chelation Therapy on Lead-induced Hepatotoxicity: A Case Series

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ABSTRACT

Background: Opium use is one of the common causes of lead toxicity. Lead poisoning can lead to hepatic, hematologic, musculoskeletal, neurological, and cardiovascular damages. In this study, we investigated the reversibility of lead-induced liver damage following chelation therapy.

Methods: We reviewed the medical records of patients with opium-induced lead poisoning regarding elevation in hepatobiliary enzymes level including Alanine Transaminase (ALT), Aspartate Transaminase (AST), and Alkaline Phosphatase (ALP) to normal level and recorded patients' age, treatment regimen, liver enzymes level before and after treatment; we also investigated other laboratory findings to rule out other causes of liver enzymes increase.

Results: We evaluated 10 male patients with the mean age of 48.3±7.42 years. All patients were referred with the chief complain of abdominal cramps (100%). The mean lead level in patients was 84.48±9.95 µg/dL. The mean serum levels of ALT, AST, and ALP significantly decreased after the treatment with chelating agents ([ALT=117.8±60.22µg/dL-76.9±40.73µg/dL, P=0.022], [AST=100.9±63.96µg/dL-69.9±37.41µg/dL, P=0.028], [ALP=449.8±234.81 µg/dL-338.3±131.22µg/dL, P=0.037]). There was no significant correlation between patients' lead level and liver enzymes level before and after the treatment.

Conclusion: The results of this study showed that the treatment with chelating agents reverses the liver injury following the lead intoxication.

1. Introduction

Lead is one of the heavy metals with no beneficial nutritional effect [1]; it is found in gasoline, paint substances, lead-contaminated opioids, and industrial, construction, and chemical materials [1-4]. The lead is absorbed by gastrointestinal and respiratory tracts and, subsequently, stores in the bone and soft tissue; about (33%) of the soft tissue sources is in the liver. The acceptable level of lead in adults is 40µg/dL and at higher concentration, the toxicity symptoms will appear [1, 3].

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The excessive amounts of lead can be replaced with trace elements and harm various tissues and organs [1]. Following the lead poisoning, gastrointestinal symptoms (including abdominal cramps, small intestinal paralysis, and constipation), kidney symptoms (such as increase in urea and creatinine following its accumulation in the cortex and medulla), as well as Central Nervous System (CNS) symptoms (such as encephalopathy) will occur [1, 3]. However, nephropathy symptoms do not appear rapidly because of the high renal capacity until (50%) of the nephrons get damaged [1].

The liver is the first organ, which receives and accumulates nutrients, xenobiotics, and medications through a portal vein in order to metabolize them. Lead intoxication has several effects on liver function such as the inhibition of heme synthesis, the reduction of estradiol-17β activity, the inhibition of metabolism through CYP450 enzymes, the reduction of aminopyrine N-demethylase activity, and increase in the activity of phase-II hepatic metabolism; they include glutathione, glutathione s-transferase, and Nicotinamide Adenine Dinucleotide Phosphate (NADPH), indicating liver nodules and carcinogenic effects of lead on the liver [3].

Lead accumulation in the liver leads to oxidative stress, increase in the lipid peroxidation, the expression of inflammatory cytokines (including TNF-alpha, the inhibition of antioxidant activity, decrease in the Adenosine Triphosphate [ATP] stores of hepatocytes), and the induction of apoptosis in Kupffer cells [3]. In this study, we plan to investigate the correlation between the lead level and increase in liver biomarkers, as well as the possibility of reversing liver damage following the treatment with chelating agents.

2. Patients and Methods

In this retrospective study, the medical records of 10 lead intoxication patients with any raising in the level of liver enzymes more than normal range were investigated between April 2014 and May 2018. The exclusion criteria included the history of other liver diseases. The patients' hepatobiliary enzymes; Alanine Transaminase (ALT), Aspartate Transaminase (AST), and Alkaline Phosphatase (ALP) were recorded at the basal hospitalization time and at the end of chelation therapy. Also, other laboratory markers including Hepatitis A Virus (HAV Ab), Hepatitis B Surface Antigen (HBsAg), Hepatitis B Core Antibody (HbsAb), Hepatitis C Antibody (HCV Ab), Human Immunodeficiency Virus (HIV), MIX, amylase, and lipase were recorded to rule out other diseases that can disrupt liver function tests including hepatitis A, B, C, HIV, and pancreatitis. Also, the patient's troponin-I level was investigated to rule out the cardiac source of AST increase.

Statistical analysis

Quantitative variables are represented as Mean±SD and qualitative variables as a percentage. In order to compare hepatic enzymes level changes before and after the treatment, the Wilcoxon test was performed. The Mann-Whitney test was used to determine the correlation between the enzymes level and treatment regimens. All statistical analyses were conducted by SPSS V. 24 (SPSS Inc., Chicago, IL, USA). P value <0.05 were considered significant.

3. Results

Ten patients with lead poisoning and impaired liver function were enrolled in the study. The mean age of the patients was 48.3±7.42 years. Patients experienced gastrointestinal symptoms including abdominal cramps (100%), constipation (30%), nausea and vomiting (20%), anorexia (10%), diarrhea (10%), as well as a neurologic symptom (seizure) (10%). None of the patients showed evidence of hepatitis A, B, C, and HIV-associated antigens or antibodies. Also, no increase was observed in troponin-I level as a marker of cardiovascular events, which impacted the AST level (Table 1). The peripheral blood sample of all patients showed the evidence of basophilic stippling, which confirmed the lead toxicity.

In the current study, the mean lead level of the patients was 84.48±9.95 µg/dL (range between 68.9 and 99.8 µg/dL). The mean level of ALT, AST, and ALP significantly decreased after treatment ([ALT=117.8±60.22µg/dL-76.9±40.73µg/dL, P=0.022], [AST=100.9±63.96µg/dL-69.9±37.41µg/dL, P=0.028], [ALP=449.8±234.81µg/dL-338.3±131.22µg/dL, P=0.037]). There was no significant correlation between the lead and enzymes level at the baseline (before the treatment) or after the treatment (P>0.05). Also, there was no significant correlation between the patients' age and level of liver enzymes release after lead poisoning, as well as their reduction after treatment (P>0.05).

4. Discussion

In recent years, occupational-associated lead poisoning has shown a dramatic reduction in industrialized societies and many other countries. Opioid-associated toxicity is considered the main cause of lead poisoning in our country in comparison with occupational causes

Table 1. Patients' chief complain, treatments, and laboratory data

No	Year	age	Chief complain	Lead level (µg/dl)	ALT1 (IU/l)	ALT2 (IU/l)	AST1 (IU/l)	AST2 (IU/l)	ALP1 (u/l)	ALP2 (u/l)	Treatment regimen	HAV Ab	HBs Ag	HBs Ab	HCV Ab	HIV.MIX	Amylase (u/L)	Lipase (IU/L)	Troponin.I
1	2018	56	Abdominal pain	93.3	87	64	51	45	510	388	D-penicillamine	Negative	Negative	200	Negative	Negative	64	32	0.1
2	2016	39	Abdominal pain +N/V	99.8	102	81	91	89	227	250	Dimaval+ CaNa2EDTA	Negative	Negative	120	Negative	Negative	25	19	<0.1
3	2016	39	Abdominal pain + Constipation	73.9	100	60	59	41	486	325	Dimaval+ CaNa2EDTA	Negative	Negative	145	Negative	Negative	30	20	<0.1
4	2016	46	Abdominal pain	92	94	39	110	47	906	340	BAL+ CaNa2EDTA	Negative	Negative	140	Negative	Negative	67	35	<0.1
5	2016	60	Abdominal pain	92.9	220	90	249	143	309	387	Dimaval+ CaNa2EDTA	Negative	Negative	207	Negative	Negative	30	31	<0.01
6	2016	45	Abdominal pain + N/V	79	202	138	155	92	287	277	Dimaval+ CaNa2EDTA	Negative	Negative	100	Negative	Negative	63	40	0.1
7	2016	58	Abdominal pain + Constipation	68.9	41	25	28	28	200	137	BAL	Negative	Negative	126	Negative	Negative	92	21	0.01
8	2016	46	Abdominal pain + Constipation	87	114	44	71	31	285	238	BAL+ CaNa2EDTA	Negative	Negative	120	Negative	Negative	66	15	0.1
9	2016	49	Abdominal pain +Anorexia	79	50	78	72	102	538	417	D-penicillamine	Negative	Negative	210	Negative	Negative	64	39	0.1
10	2014	45	Abdominal pain+ seizure+ diarrhea	79	168	150	123	81	750	624	BAL+ CaNa2EDTA + Succimer	Negative	Negative	222	Negative	Negative	70	53	<0.01

N/V: Nausea and Vomiting; ALT: Alanine Transaminase (ALT1: Before treatment, ALT2: After treatment); AST: Aspartate Transaminase (AST1: Before treatment, AST2: After treatment); ALP: Alkaline Phosphatase (ALP1: Before treatment, ALP2: After treatment); HAV.Ab: Hepatitis A Virus Antibody; HBS.Ag: Hepatitis B Virus Surface Antigen; HBS.Ab: Hepatitis B Virus Surface Antibody(IU/L); HCV.Ab: Hepatitis C Virus Antibody; HIV: Human Immunodeficiency Viruses; BAL: British anti-Lewisite

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[5]. Lead poisoning disrupts cardiovascular, hematopoietic, neurological, and renal function [2, 4-7]. Acute lead poisoning requires exposure to higher concentrations of lead compared to chronic poisoning (100-200 µg/dL vs. 40-60µg/dL) [8]. The acute symptoms of lead poisoning commonly include gastrointestinal signs and symptoms such as abdominal colic, back pain, nausea, vomiting, anorexia, and constipation. Lead toxicity is one of acute abdominal pain differential diagnosis [2, 5]. The lack of gastrointestinal symptoms can reduce the doubt of the medical team regarding the lead poisoning; in the current report, all of 10 patients were referred with gastrointestinal complications. The other symptoms of acute intoxication include muscular symptoms such as fatigue, weakness and pain, and neurological symptoms like headache, irritability, sleep disorders, neuropathy, seizure, and coma. In chronic exposure, which presents in low-concentration exposure in the long term, clinical symptoms such as persistent vomiting, encephalopathy, and coma may appear [5, 8].

Subacute toxicity may lead to changes in the morphology and function of hepatocytes, bile pigmentation disorders, hemosiderosis of Kupffer cells, hepatitis, and even necrosis of liver cells. It induces cellular growth factors function including TGFα1 and TGFβ, causes cellular proliferation and hyperplasia, and leads to the development of neoplasia [3]. Also, high lead level induces oxidative stress in red blood cells, distributes heme synthesis cycle, the production of abnormal erythrocytes, the deposition of iron in endoplasmic reticulum system and the decrease in the iron-binding capacity [2].

The lead induces lipid peroxidation and depletion of glutathione deposits, especially in Kupffer cells, and disrupts hepatocytes functions, membrane transportation, and cellular metabolism. Lead enters the liver through binding to plasma proteins and disrupts the function of the enzyme involved in the DNA, RNA, and proteins synthesis. It interrupts the liver protein synthesis such as albumin and increases the serum level of some enzymes such as ALT, AST, ALP, and lactate dehydrogenase [3, 6, 9]. A study shows that the elevation of ALP and lactate dehydrogenase occurred at a lead level above 78µg/dL, but not in lower concentrations [3].

As in our study, the patients with higher lead level showed a higher level of enzymes release after intoxication (Table 1). One study demonstrates that lead causes a dose-dependent increase in ALT level in patients with no evidence of hemochromatosis, viral hepatitis, or alcoholic hepatic injury [10]. However, there was no correlation between lead concentration and hepatobiliary enzymes level before or after the treatment in our patients (P>0.05). Chang et al. introduced ALT and Gamma-Glutamyl Transferase (GGT) as hepatic injury biomarkers before irreversible changes [10]. Sreeram et al. also explained that GGT is a marker for the evaluation of liver oxidative stress [11]. However, in our study, this maker was only examined in 1 patient, showing an upward trend (patient N-10, GGT [before treatment]=89U/L).

The treatment of lead toxicity is based on chelating agents including Succimer, Dimercaprol British Anti-Lewisite (BAL), DMSA, CaNa2EDTA, and D-penicillamine. However, BAL is not recommended to be used alone because of its ability to cross from the blood-brain barrier, the possibility of redistribution, and unpleasant effects such as nausea, vomiting, fever, hypertension, and tachycardia. Many experts recommend combination therapy of BAL and CaNa2EDTA, especially in severe cases [12, 13]. In our study, 1 patient received only BAL because of the unavailability of Succimer or CaNa2EDTA.

The results of this study indicate that the treatment with chelating agents reduces the liver enzymes level and restores liver damage following lead poisoning so that the levels of liver enzymes significantly decreased in these patients after treatment (P<0.05). Only one of the penicillamine-treated patients experienced a slight increase in ALT and AST level. Wollheim and Lindstrom in their study stated that penicillamine can increase ALT, AST, ALP, and lactate dehydrogenase level, which can reverse with its discontinuation. However, they reported evidence of histological and inflammatory changes [14].

5. Conclusion

Overall, in this study, we observed that the treatment with chelating agents significantly decreased the levels of hepatobiliary enzymes in patients with opium associated-lead poisoning. However, subsequent histological studies are also needed to investigate the effects of these treatments on the long-term changes of liver tissue.

Ethical Considerations

Compliance with ethical guidelines

There was no ethical considerations to be considered in this research.

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Author's contributions

Statistical analysis of data: Mahmood Moosazadeh; Data collection and preparation of the manuscript: Faeze Shadfar, Zakaria Zakariaei, Seyed Khosro Ghasempoori, Mahmood Moosazadeh, Navid Khosravi.

Conflict of interest

The authors declared no conflict of interest.

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