Original Article

Evaluation of Thallium Levels in Opioid Substance Users: A Case–Control Study

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Abstract

Aims: Drug abuse is one of the major problems threatening human health. The presence of heavy metals (e.g., lead and thallium) in illicit drugs has raised concerns. This study was designed and performed to indicate the status of thallium in the urine of opioid users with symptoms similar to thallotoxicosis and compare them with the control group. **Materials and Methods:** This case–control study was conducted in Kashan with the participation of 200 people (including 100 people in the opioid user group and 100 people in the control group). Then, electrothermal atomic absorption spectrometry was used to determine the concentrations of urinary thallium. **Findings:** In the opioid group, the median (interquartile range) urinary thallium concentrations was 72/29 ± 49/33 µg/l, whereas in the control group, it was 5/57 ± 3/015 µg/l. There was a significant difference in the concentrations of urinary thallium between the opioid group and the control group. Furthermore, the prevalence of thallotoxicosis-related clinical symptoms was significantly higher in the opioid group with high urinary thallium concentrations compared with the control group (weakness, fatigue, paresthesia, ataxia, vertigo, memory deficits, tremor, aggressiveness, tinnitus, sweating, rashes, dry skin, constipation, nausea, vomiting, abdominal pain, and diarrhea). **Conclusions:** The results of the present study indicated that the levels of urinary thallium in patients using illicit opioids are significantly higher, which can be due to contamination of drugs with thallium.

Keywords: Opioids, substance use, thallium

Introduction

Substance abuse is one of the most important health threats in the world.[1] Opioid use disorder is a chronic reversible disorder that leads to health problems. This disorder is first triggered by the activation of brain reward circuits and then increasingly affects anti-reward circuits, leading to undesirable emotional states and relapse.[2,3] The history of opium use in Iran dates back to at least three centuries ago and is one of the most widely used drugs.[1,4,5] Reports indicate that poisoning and overdose are the most important factors in admission and hospitalization of opium users in hospitals in Iran.[4,6]

Thallium is classified as a rare trace element.[7,8] The toxic amount of thallium is 8 mg/kg and the lethal amount is 10–15 mg/kg. Thallium can cause kidney, central nervous system, and heart disorders that can eventually lead to death.[9,10] Although the exact mechanisms of thallotoxicosis are not yet fully understood, the proposed mechanisms include potassium ion replacement in most biological processes and the capacity of thallium to react with thiol groups. In general, thallium appears to inhibit a wide range of interference with vital metabolic processes and enzyme reactions (sulfhydryl groups) that ultimately upset cell balance and lead to general intoxication.[11] The presence of thallium in urine and hair can indicate contact with thallium. Urine test for thallium can be

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detected up to 8 weeks, and the normal amount of thallium in urine is <1 ppm.[12] The main features of thallotoxicosis include gastroenteritis, peripheral neuropathy, and alopecia (treatment may be ineffective at this stage).[13,14]

Thallotoxicosis can be difficult to diagnose because it is not usually suspected.[14] On the other hand, it has been reported that thallotoxicosis can occur in drug users (heroin and opioids),[15-18] which indicates the importance of conducting more and more comprehensive studies in this issue. to detect the presence of thallium in urine samples of opioid abusers and it is linked to common symptoms and signs of thallotoxicosis. Thallium levels in urine were evaluated in both groups using electrothermal atomic absorption spectrometry. Our findings demonstrated that thallium levels in urine significantly higher were in opioid substance users than control group.

Materials and Methods

This is a case–control study. This study included 100 opioid users (for example, users of heroin, opium residue, opium, and mix-users) as a study group and 100 people without a history of drug use as a control group (immunoassay tests were used to confirm the presence of morphine in urine to confirm opioid abuse). The age range of the participants was 18–90 years, and the users of acetaminophen and codeine, tramadol, and diphenoxylate were excluded from the study. Cases with a history of thallium exposure (e.g., painters, solderers, and battery makers) were also excluded. Samples taken from participants included 8 ml of a 24-h urine sample (both opioid and control groups). After receiving, the samples were stored at-20°C until the experiment. In order to measure the levels of thallium, an atomic absorption device (A Perkin Elmer [Model: 3030]) was used. We also used PerkinElmer grooved graphite tubes (pyrolytically coated) for the experiment. At all stages, the samples remained confidentially coded. To measure thallium, we first added nitric acid (0.5 mL), sulfuric acid 1% (0.5 mL), and Triton X-100 (10 mL) to urine, blank, and standard samples. After all the samples were well centrifuged and vortexed (2 min), 200 µl of modifier solution was added and centrifuged again for another 2 min, and finally, 25 µl of the top layer of solution was injected into the graphite tube. Thermal program for thallium determination was the following: 130°C initially for drying, 300°C (for ashing of organic compounds), 600°C (for decomposition of inorganic compounds), and 1700°C (for atomization). Detection limits of 0.2 µg/L, accuracy of 97.4%, and precision of 3.65% were obtained through repeated analysis of reference biological materials (SERONORM/level 2, lot 1011645).[19] SPSS 17 software (SPSS Inc, IL, USA) was used for statistical analysis. The Mann–Whitney *U*-test was used for quantitative data, and the *t*-test was used for independent data. Qualitative information was analyzed by Fisher test, and the relationship among variables was examined by Spearman correlation. A value of $P < 0.05$ was considered statistically significant. This study was conducted in accordance with the Helsinki Declaration. After receiving approval from the Ethics Committee of Kashan University of Medical Sciences (IR.KAUMS.MEDNT.REC.1398.015), the study was explained to the participants and their consent was obtained.

Results

In this study, 200 people were studied (100 in the control group and 100 in the opioid group), of which 197 (98.5%) were male and 3 (1.5%) were female. The mean ± standard deviation (SD) of the participants' age (age range: 18–90) was equal to 45.82 ± 13.32. The mean ± SD of urinary thallium levels in all participants was 38.93 ± 48.3 µg/l (1.2–266.7 µg/l). Furthermore, the median (interquartile range) concentrations of urinary thallium for the opioid group and the control group were 72/29 ± 49/33 and 5/57 ± 3/015 µg/l, respectively, which was significantly higher in the opioid group ($P < 0.001$). The data showed that the levels of urinary thallium in both age groups (50< years [$P < 0.001$] and ≥50 years [$P < 0.001$]) were significantly higher in the opioid users. Furthermore, the levels of urinary thallium in men in the opioid group were significantly higher than men in the control group ($P < 0.001$). On the other hand, the results did not show any significant relationship between smoking duration, type of drug use, duration of use, and route of use with urinary thallium levels in the opioid group [Table 1 and Figure 1].

The data indicated that the incidence and prevalence of symptoms and signs of thallotoxicosis are higher in the opioid group than in the control group [statistical information is in Tables 2-4]. Symptoms such as weakness ($P < 0.001$), fatigue ($P < 0.001$), paresthesia ($P < 0.001$), ataxia ($P < 0.001$), vertigo ($P < 0.001$), memory deficits ($P < 0.05$), tremor ($P < 0.001$), aggressiveness ($P < 0.01$), tinnitus ($P < 0.001$), sweating ($P < 0.001$), rashes ($P < 0.001$), dry skin ($P < 0.001$), constipation ($P < 0.001$), nausea ($P < 0.001$), vomiting ($P < 0.001$), abdominal pain ($P < 0.001$), and diarrhea ($P < 0.05$) were significantly higher in the opioid group.

Discussion

Thallium is one of the most toxic metals.[7] Contamination with low amounts of thallium can occur from exposure to the natural environment, water, fruits, crops, or livestock.[20] On the other hand, reports have suggested that illegal drugs may contain impurities of thallium, lead, and steroids.[15,16,21]

In the present study, we examined urinary thallium levels in opioid users. Our results showed that the levels of thallium in the urine of the opioid group were significantly higher compared to the control group. Furthermore, in our studies, we saw many symptoms of thallotoxicosis in opioid users, which were significantly higher in the opioid group compared to the control group (these symptoms are shown in three categories: neurological, dermatological, and gastrointestinal). Although thallium levels in illicit drugs are low, when taken in high doses, they can lead to clinical symptoms of thallotoxicosis.[18] Few studies report unusual thallotoxicosis in illegal drug users.[15-18]

Table 1: General characteristics of the study participants and urinary thallium concentrations in the opioid group and the control group (μg/L)[a]

Variable	Opioid group (*n*=100)	Control group (*n*=100)	*P*
Age (year)[b]	45.98±15.46	45.67±10.83	0.721
Gender, *n* (%)[c]			
Male	99 (99)	98 (98)	1
Female	1 (1)	2 (2)	
Urinary thallium level[d] (g/L)	72.29±49.33	5.57±3.01	<0.001
Urinary thallium level by age (μg/l)			
<50 years	72.49±49.25	4.88±2.49	<0.001
≥50 years	71.99±50.07	6.66±3.44	<0.001
Urinary thallium level by sex (μg/l)			
Male	71.44±48.83	5.59±3.01	<0.001
Female	-	5.30±3.96	0.221
Urinary thallium levels in opioid users based on smoking duration (μg/l)			
>20 years (*n*=35)	68.28±54.79	-	0.914
≥20 years (*n*=39)	65.86±40.87	-	
Urinary thallium levels in opioid users based on the type of drug used (μg/l)			
Opium (*n*=66)	76.28±52.14	-	0.416
Heroin (*n*=11)	79.89±49.20	-	
Methamphetamine (*n*=2)	52.70±7.77	-	
Different drugs (*n*=21)	57.62±40.59	-	
Urinary thallium levels in opioid users based on duration of drug use (μg/l)			
<20 years (*n*=55)	76.31±52.20	-	0.281
≥20 years (*n*=45)	67.38±45.67	-	
Urinary thallium levels in opioid users based on consumption routes (μg/l)			
Smoking (*n*=61)	67.42±43.75	-	0.736
Oral (*n*=29)	80.62±57.41	-	
Smoking and oral (*n*=6)	86.33±59.69	-	
Different ways (*n*=4)	65.12±60.78	-	

[a]Data are mean±SD and percentage, [b]Obtained from independent samples *t*-test, [c]Obtained from Fisher's exact test, [d]Obtained from Mann–Whitney U-test/ significance level *P*<0.05. SD: Standard deviation

In 2015, Ghaderi *et al*. reported that the average amount of urinary thallium in opioid-poisoned subjects was 21 μg/L, which was significantly higher than the control group (1 μg/L).[15] Another study also confirmed the significant presence of thallium in the hair, blood, and urine of opioid users.[18] Thallium contamination is not limited to opioid users. Other studies have reported that thallotoxicosis has occurred in heroin users.[16,17] In fact, one of the reasons for illegal drug contamination with thallium can be due to the addition of heavy metals (e.g., lead and thallium) to drugs by smugglers and salesmen to increase the weight of the drug.[16,19,22]

The results of our study indicated that a range of clinical symptoms and signs, such as the symptoms of thallotoxicosis, may be seen in users of illicit opioids. The most common symptoms observed in opioid users were weakness, fatigue, paresthesia, ataxia, vertigo, memory deficits, tremor, aggressiveness, insomnia, tinnitus, scalp hair loss, sweating, rashes, constipation, abdominal pain, nausea, dry skin, vomiting, and diarrhea. These findings are consistent with the results of other studies, but in some cases, there are differences.[15,18,23] For example, in the study of Ghaderi *et al*., seizures (or a history of seizures) mentioned one of the common symptoms in opioid users, whereas in the present study, seizures were not significantly different in the opioid group with the control group. Seizures can be a side effect of tramadol or other illicit drugs in opioid users (to achieve euphoria or as an opiate replacement).[15,24,25] Therefore, it should be considered that the difference in some clinical symptoms can be due to other factors such as the use of other drugs[26] or smoking.[27,28]

Our findings suggest that illegal opioids may be a source of exposure with thallium. On the other hand, these results and the results of similar studies can help diagnose the symptoms of thallotoxicosis in opioid patients.

In the present study, we had some limitations. One of these limitations was the lack of access to matched controls in some cases. Other examples include sample size (for better results, a larger sample size is required). On the other hand, in the opioid group, we were not able to accurately identify the source of thallium in smokers, and it is suggested that future studies measure the amount of thallium in smokers separately. Finally, although in this study, we tried to examine only opioid users, it was not possible to verify what drugs they had used in the past.

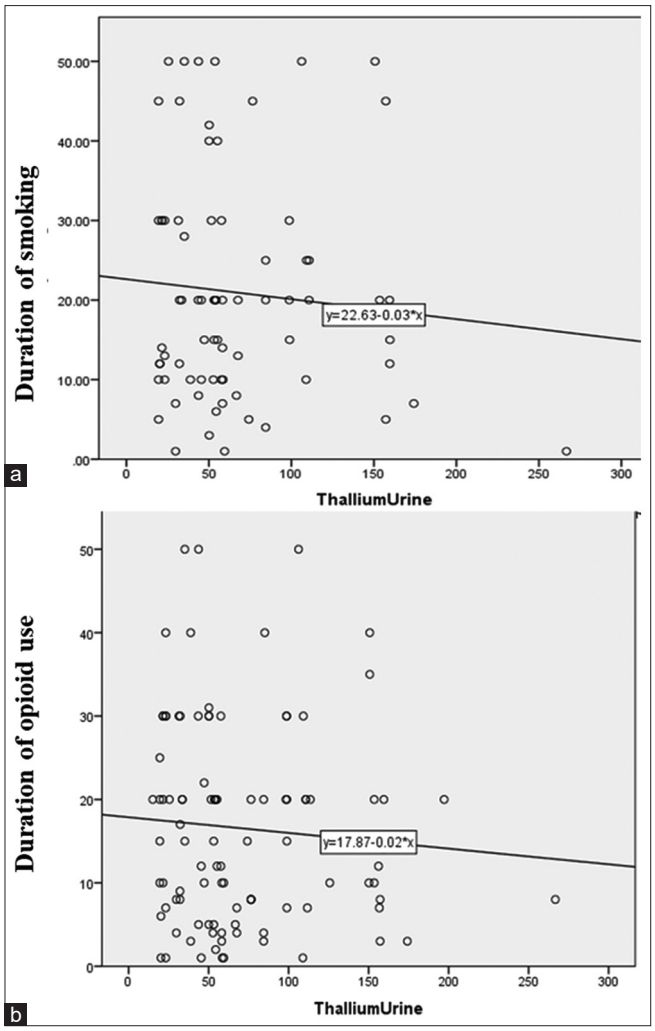

Figure 1: (a) Correlation between smoking duration and urinary thallium concentration (μg/L) and (b) Correlation between duration of opioid use and urinary thallium concentration (μg/L)

Conclusions

In general, it was found that urinary thallium levels in opioid users are higher than normal. Therefore, there is a need to monitor the health of opioid users (especially users of substances produced by illegal centers) and check the levels of thallium in them and, if necessary, taken to treat and diagnose these patients.

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Table 2: Frequency of neurological signs and symptoms in the opioid group and the control group

Clinical symptoms	Frequency (%)			*P*
Neurological signs and symptoms	Opioid group, *n* (%)	Control group, *n* (%)	Total, *n* (%)	
Weakness	72 (72)	15 (15)	87 (43.5)	<0.001
Fatigue	69 (69)	8 (8)	77 (38.5)	<0.001
Paresthesia	41 (41)	5 (5)	46 (23)	<0.001
Ataxia	20 (20)	2 (2)	22 (11)	<0.001
Vertigo	28 (28)	8 (8)	36 (18)	<0.001
Blurred vision	12 (12)	8 (8)	20 (10)	0.346
Memory deficits	20 (20)	10 (10)	30 (15)	<0.05
Tremor	33 (33)	5 (5)	38 (19)	<0.001
Aggressiveness	40 (40)	20 (20)	60 (30)	<0.01
Jerking movements	3 (3)	0	3 (1.5)	0.246
Insomnia	4 (4)	22 (22)	26 (13)	<0.001
Seizures	9 (9)	2 (2)	11 (5.5)	0.058
Depression	31 (31)	23 (23)	54 (27)	0.203
Tinnitus	23 (23)	4 (4)	27 (13.5)	<0.001
Delirium-psychosis coma	3 (3)	0	3 (1.5)	0.246
Headache	41 (41)	29 (29)	70 (35)	0.075
Emotional liability	11 (11)	4 (4)	15 (7.5)	0.105

Table 3: Frequency of dermatological signs and symptoms in the opioid group and the control group

Clinical symptoms	Frequency (%)			*P*
Dermatological signs and symptoms	Opioid group, *n* (%)	Control group, *n* (%)	Total, *n* (%)	
Scalp hair loss	19 (19)	38 (38)	57 (28.5)	<0.01
Body hair loss	1 (1)	0	1 (0.5)	1
Sweating	56 (56)	8 (8)	64 (32)	<0.001
Rashes	13 (13)	0	13 (6.5)	<0.001
Dry skin	30 (30)	7 (7)	37 (18.5)	<0.001
Mees' lines	4 (4)	0	4 (2)	0.121
Palmar erythema	1 (1)	0	1 (0.5)	1
Acne	11 (11)	4 (4)	15 (7.5)	0.105

Table 4: Frequency of gastrointestinal signs and symptoms in the opioid group and the control group

Clinical symptoms	Frequency (%)			*P*
Gastrointestinal signs and symptoms	Opioid group	Control group	Total	
Constipation	67 (67)	14 (14)	81 (40.5)	<0.001
Abdominal pain	59 (59)	4 (4)	63 (31.5)	<0.001
Nausea	44 (44)	2 (2)	46 (23)	<0.001
Vomiting	36 (36)	2 (2)	38 (19)	<0.001
Diarrhea	11 (11)	2 (2)	13 (6.5)	<0.05

Conflicts of interest

There are no conflicts of interest.

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