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Survey on Hypothermia and Hyperthermia in Poisoned Patients in a Unique Referral Hospital, Tehran, Iran

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Abstract

Background: Body temperature is a critical criterion of health. Drugs and a variety of poisons can affect body temperature in poisoned patients, causing hyperthermia and hyperpyrexia.
Objectives: Our previous study's findings in patients poisoned with organophosphate led us to the goal of this study: obtaining the initial tympanic temperature in patients poisoned by a variety of toxins.
Materials and Methods: A cross-sectional study reviewed the records of poisoned patients who were admitted to the toxicological intensive care unit (TICU) at Loghman Hakim hospital poison center (LHHPC) from February 2014 to February 2015. The data collected included gender, age, type of poisoning, the season during which poisoning occurred, vital signs, initial tympanic temperature (first four hours), presence of seizures, white blood cell (WBC) count, creatinine phosphokinase (CPK), length of stay and patient outcome. We determined the mean (SD) for normally distributed continuous variables, the median and interquartile range for non-normally distributed continuous variables, and the absolute and relative frequency (%) for categorical variables. All were determined using SPSS version 16.
Results: Data were collected from 310 eligible patients. The mean patient age was 32.65 (with a standard deviation of 14.40). Of the patients in the study, 183 (59%) were male. Intentional poisoning in an attempted suicide was documented in 253 (81.6%) patients. The most prevalent poisoning agent was aluminum phosphate (18.70%), followed by methadone (10%) and opium (10%). Seventy percent of the patients (n = 217) were diagnosed and classified with fever or hyperthermia. A temperature $\geq$ 40°C was detected in just three cases. The highest mean temperature was found in patients poisoned with amphetamine, organophosphate and tramadol. Patients with alcohol and phenobarbital poisoning were included in the sample, but these patients were not diagnosed with hypothermia. WBC $\geq$ 10,000 cells/mL and CPK $\geq$ 975 IU/L were recorded in 57.7% and 13.2% of subjects, respectively.
Conclusions: Body temperature changes in human poisonings are a matter in need of special attention. A literature review did not reveal any controversy over hypothermia, but poisoning cases exhibit a variety of patterns of fever and hyperthermia. If there are no limits to the diagnosis of fever and hyperthermia, all cases with a poor prognosis which fail to respond to treatment could be categorized as drug-induced hyperthermia. Therefore, a different approach is needed for poisoning cases.

Keywords: Hypothermia, Hyperthermia, Poisoning

1. Background

The hypothalamus is responsible for body temperature, which is a critical criterion of health. Average temperature in humans varies due to a variety of factors, including the patient's condition and medical diagnosis and treatment. There is no consensus on the normal range of temperature. Normal values range from 37.5 to 38.3°C (99.5 to 100.9°F) (1, 2). However, some studies report 36.8°C (98.2°F) as the mean body temperature (oral) in healthy individuals, with a spectrum of 35.6°C (96°F) to 38.2°C (100.8°F) and trivial daily variation (3). However, the mean normal body temperature is defined 36.8°C $\pm$ 0.4 in a textbook of internal medicine (4).

The definition of a fever is, therefore, controversial. A body temperature above 37.2°C in the morning or above 37.7°C in the evening indicating that the hypothalamus has increased the core body temperature set point, or its threshold is defined as a fever (4). Fever commonly occurs in approximately one-half of the patients admitted to intensive care units. It may be attributed to either infectious or noninfectious causes such as adrenal insufficiency and drug fever. The development of a fever increases the risk of

death in critically ill adults (4, 5).

Hyperthermia is defined as an uncontrolled rise of core body temperature above 37°C, at which temperature the human body is unable to lose heat (4). Exposure to warm or humid environments and some medications can cause hyperthermia or fever (5).

Millions of people suffer from poisoning by various illicit substances or medications annually. Mortality due to complications from poisoning has increased dramatically in recent years. In the United States, mortality rates from unintentional poisoning almost tripled from 1990 to 2002 (6).

Drugs and the type of poison and its toxicity can affect body temperature in poisoned patients. Some potential poisons, such as ethanol, phenothiazines, barbiturates, antidepressants and organophosphate, induce hypothermia, and some, such as amphetamines, methamphetamine, MDMA ("ecstasy"), cocaine, salicylates, lithium, anticholinergics and monoamine oxidase inhibitors, induce hyperthermia (4, 7, 8).

Other studies have reported different findings from ours. In our previous study, the body temperatures of patients poisoned with organophosphate (OP) were significantly different from those reported in most other studies. However, we did not detect any hypothermia in poisoned patients (7, 9, 10).

2. Objectives

The findings of our previous study led us to the goal of this study: obtaining the initial tympanic temperature in a number of poisoned patients.

3. Materials and Methods

3.1. Study Design and Population

All poisoned patients who were admitted directly from the toxicological emergency room to the toxicological intensive care unit in Loghman Hakim hospital poison center (LHHPC) from February 2014 to February 2015 were included in this cross-sectional descriptive study. We used census sampling in this survey. All patients (n = 11) with underlying diseases, immune deficiency, or a history of infectious diseases or antibiotic use were excluded.

The hospital is a unique care teaching and referral poison treatment center in Tehran that treats, on average, nearly 20,000 patients annually. This study was approved by the ethics committee of Shahid Beheshti University of Medical Sciences (research project No.: 167.24.12.1393).

Data were retrospectively collected from patient records by a trained nurse, who filled out questionnaires with information including patient gender, age, type of poisoning, the season, presence of seizures, respiratory rate, pulse rate, blood pressure, initial tympanic temperature (first four hours), leukocyte count (cells/mL), amount of creatinine phosphokinase (CPK), length of stay and patient outcome.

3.2. Definitions

We used tympanic thermometers to measure patient temperature. The thermometers were calibrated repeatedly to assure validity. In this study, a tympanic temperature (TT) between 35.4 and 37.8°C was considered normal (11).

A TT above 37.8°C was considered a fever (12, 13).

Rhabdomyolysis was diagnosed when CPK was measured at more than five times the normal amount ($\geq$ 975 IU/L) (14).

3.3. Statistical Analysis

A descriptive statistical analysis was performed using the mean (SD) for continuous variables and the absolute and relative frequency (in percentages) for categorical variables. The median and interquartile range was reported for non-normal variables. The statistical analysis was performed using SPSS version 16 (SPSS Inc., Chicago, IL, USA).

4. Results

Three hundred and ten patients were enrolled in this retrospective study. The patients' eligibility for the study was determined from a review of their medical records. The mean age of the patients was 32.65 (SD $\pm$ 14.40). Of these, 183 (59%) were male and 127 (41%) were female.

Table 1 shows the baseline characteristics of the patients. Intentional poisoning in a suicide attempt was recorded in 253 (81.6%) patients, and 57(18.4%) were cases of accidental toxicity. Aluminum phosphate (ALP) (58 patients), opium (31 patients) and methadone (31 patients) were the types of poisons most frequently found in patients in this study (Table 2). Overall, the mean TT was 37.71°C (SD $\pm$ 0.62), with a range of 36 - 41.3°C. Seventy percent of the patients (n = 217) were classified as having a fever or hyperthermia. Surprisingly, hypothermia was not reported in this study, although the study included cases of alcohol and phenobarbital poisoning. A temperature $\geq$ 40°C was detected in just three cases of patients with amphetamine (n = 2) or phenobarbital (n = 1) poisoning. The maximum mean temperature was 38.2°C in cases of amphetamine poisoning, 38.1°C in cases of organophosphate poisoning and 38°C in cases of tramadol poisoning (Table 2).

Table 1. Baseline Characteristics of the Poisoned Patients (n = 310)

Variables	Values[a]
Age	32.65 ± 14.40
Min-Max	4 - 78
Sex	
Male	183 (59)
Female	127 (41)
Cause of poisoning	
Suicide	253 (81.6)
Accidental	57 (18.4)
Season	
Spring	109 (35.2)
Summer	108 (34.8)
Autumn	27 (8.7)
Winter	66 (21.3)
Intubation	
Yes	262 (84.5)
No	48 (15.5)
Seizure	
Yes	23 (7.4)
No	287 (92.6)
Hypertension	
Yes	47 (15.2)
No	263 (84.8)
Pulse Rate	95.42 ± 23.31
Min-Max	39 - 178
Respiratory Rate	18.44 ± 3.84
Min-Max	12 - 26
Creatinine	1.29 ± 0.9
Min-Max	0.5 - 14.9
Creatinine phosphokinase[b]	150 ± 340
Min-Max	20 - 12788
White blood cells[b]	10800 ± 6700
Min-Max	1700 - 36,600
Hemoglobin	13.72 ± 1.96
Min-Max	7.1 - 18.9
Creatinine phosphokinase	
CPK > 975	269 (87.3)
975 ≤ CPK < 10,000	39 (12.6)
Cpk ≥ 10000	2 (0.6)
White blood cells	
WBC ≤ 4000	4 (1.3)
4000 < WBC > 10,000	127 (41)
WBC ≥ 10000	179 (57.7)
Outcome	
Expire	50 (16.1)
Cure	260 (83.9)

[a] Values are expressed as No. (%) or mean ± SD.
[b] Median (Interquartile range).

The two amphetamine poisoning cases had a leukocyte count of 8,800 and 17,000; the respective CPK measurments of those cases were 3675 and 150. The leukocyte count of the phenobarbital case was 15200, and the CPK count was 4340 (Table 3). A CPK greater than 975 IU/L was recorded in 13.2% (n = 41) of cases (Table 3). A CPK over

Table 2. Patients' Tympanic Temperature in the First Four Hours Divided by Type of Poisoning

Type of Toxicity	Number	Mean ± SD	Max	Min
Total	310	37.71 ± 0.62	41.3	36
Aluminum phosphate	58	37.45 ± 0.42	38.1	36.7
Co	5	37.76 ± 0.56	38.7	37.2
Phenytoin	10	37.94 ± 0.75	39.2	36.7
Methadon	31	37.73 ± 0.49	39	36.7
Organophosphate	18	38.06 ± 0.53	39.2	37.2
Carbamazepin	15	37.84 ± 0.71	39.3	36.7
Tricyclic antidepressants	13	37.87 ± 0.54	38.7	36.9
Phenobarbiotal	16	37.81 ± 0.71	40	36.7
Benzodiazepine	30	37.49 ± 0.49	38.7	36
Opium	31	37.54 ± 0.48	39.2	36.7
Amphetamin	20	38.25 ± 1.15	41.3	36.7
Acetaminophen	28	37.67 ± 0.47	38.7	36.7
Methanol	17	37.55 ± 0.58	38.5	36.7
Tramadol	18	38.03 ± 0.64	39.2	36.7

10,000 was reported in just two patients: those poisoned by methadone and phenytoin.

5. Discussion

Since there have been a variety of findings in the literature on the relationship between body temperature and poisoning, we decided to investigate this issue in great detail. It seems that ours is the first study investigating body temperature in cases of poisoning by different kinds of poisoning.

According to the worldwide database, ethanol, phenothiazines, barbiturate and antidepressants are considered to be toxicological risk factors for hypothermia (4). Hypothermia has been identified as an early symptom of phenobarbital and methanol or ethanol poisoning, but this finding was not supported by the present study. Most of the patients in our study presented with hyperthermia rather than hypothermia. Rhabdomyolysis may be a cause of fever in cases of phenobarbital poisoning. Also, in this study, hypothermia was not diagnosed in every type of poisoning. As mentioned previously, the patient poisoned with organophosphate did not experience hypothermia (15). A study by Moffatt et al. reported early hypothermia (body temperature < 35°C) in half of the patients poisoned by OP and vice versa (16). It seems that the lack of hypothermia in this study is due to atropinization prior to hospitalization and to the tropical climate in which the study was carried out (15).

Both hyperthermia and fever cause an increase in core body temperature; however, their underlying mechanisms and treatments are different (4, 15). Excessive use of drugs and natural compounds that affect the thermoregulatory system may induce or contribute to hyperthermia. Hyperthermia associated with drug overdose is dangerous and potentially lethal.

It is notable that more than two-thirds of the patients in this study were diagnosed and classified with a fever or hyperthermia, but body temperatures above 40°C were reported just in 3 (1%) cases. Patients poisoned with amphetamine, organophosphates and tramadol had the highest mean body temperature. Of these toxins, only amphetamine could reasonably be assumed to cause drug-induced hyperthermia, although the other toxins also demonstrated a tendency to increase body temperature (4, 8). Our observations strongly emphasized the difference in body temperature changes between Iranian patients and those from other countries (4, 15).

The location of the patients in the hospital, the room's temperature, specialized mattresses, hot lights, air conditioning and dialysis may have also influenced patient body temperatures (15, 17). Most of the poisoning cases in this study occurred in spring and summer. Furthermore, the cases in the study occurred in tropical regions: south Asia, the middle east and Africa (16). Ambient temperatures could explain the high body temperatures in our hospitalized patients.

On the other hand, in the current study, 57.7% of the pa-

Table 3. [Part 1] Distribution of Patients Based on the Creatinine Phosphokinase and Leukocyte Levels, Type of Toxicity and Normal or High Temperature[a]

Type of Toxicity/LAB Findings	35.4 ≤ TT > 37.8 Normal[b]	37.8 ≤ TT < 40 Fever/Hyperthermia
ALP		
CPK < 975	23 (39.7)	34 (58.6)
975 ≤ CPK < 10,000		1 (1.7)
WBC ≤ 4000		
4000 < WBC > 10,000	9 (15.5)	11 (19)
WBC ≥ 10,000	14 (24.1)	24 (41.1)
phenytoin		
CPK < 975	2 (20)	7 (70)
975 ≤ CPK < 10,000		
Cpk ≥ 10,000		1 (10)
WBC ≤ 4000		
4000 < WBC > 10000	1 (10)	3 (30)
WBC ≥ 10,000	1 (10)	5 (50)
Organophosphate (n = 18)		
CPK < 975	1 (5.6)	17 (94.4)
975 ≤ CPK < 10,000		
WBC ≤ 4000		
4000 < WBC > 10,000	1 (5.6)	6 (33.3)
WBC ≥ 10,000		11 (61.1)
Tricyclic antidepressants (n = 13)		
CPK < 975	3 (23.1)	10 (76.9)
975 ≤ CPK < 10,000		
WBC ≤ 4000		1 (7.7)
4000 < WBC > 10,000	2 (15.4)	7 (53.8)
WBC ≥ 10,000	1 (7.7)	2 (15.4)
Methanol (n = 17)		
CPK < 975	4 (23.5)	9 (52.9)
975 ≤ CPK < 10,000	2 (11.8)	2 (11.8)
WBC ≤ 4000		
4000 < WBC > 10,000	1 (5.9)	4 (23.5)
WBC ≥ 10,000	5 (29.4)	7 (41.2)
Amphetamine (n = 20)[c]		
CPK < 975	4 (20)	11 (55)
975 ≤ CPK < 10,000	1 (5)	2 (10)
WBC ≤ 4000		
4000 < WBC > 10,000	2 (10)	2 (10)
WBC ≥ 10,000	3 (15)	11 (55)
Tramadol (n = 18)		
CPK < 975	3 (16.7)	11 (61.1)
975 ≤ CPK < 10,000		4 (22.2)
WBC ≤ 4000		1 (5.6)
4000 < WBC > 10,000	3 (16.7)	3 (16.7)
WBC ≥ 10,000		11 (61.1)

[a] Values are expressed as No. (%).
[b] There was not any hypothermia.
[c] There were three reports of temperature ≥ 40°C in the patients poisoned with amphetamine (n = 2) or phenobarbital (n = 1), which are not shown in this table.

tients had a leukocyte count over 10000 when admitted, and 72.6% of them were febrile. Fever in these patients may be explained by infection, but mild leukocytosis is a normal symptom in poisoned patients. More than 50% of the patients poisoned with opioid or methadone had leukocytosis. In poisoned addicts, fever and hyperthermia may be caused by infection or by impurities in the substance or drug (18, 19).

Table 3. [Part 2] Distribution of Patients Based on the Creatinine Phosphokinase and Leukocyte Levels, Type of Toxicity and Normal or High Temperature[a]

Type of Toxicity/LAB Findings	35.4 ≤ TT > 37.8 Normal[b]	37.8 ≤ TT < 40 Fever/Hyperthermia
Co		
CPK < 975	1 (20)	4 (80)
975 ≤ CPK < 10,000		
WBC ≤ 4000		
4000 < WBC > 10,000		2 (40)
WBC ≥ 10,000	1 (20)	2 (40)
Metadon		
CPK < 975	5 (16.1)	16 (51.6)
975 ≤ CPK < 10,000	4 (12.9)	5 (16.1)
Cpk ≥ 10,000		1 (3.2)
WBC ≤ 4000		
4000 < WBC > 10,000	4 (12.9)	8 (25.8)
WBC ≥ 10,000	5 (16.1)	14 (45.2)
Carbamazepin (n = 15)		
CPK < 975	4 (26.7)	10 (66.7)
975 ≤ CPK < 10,000		1 (6.7)
WBC ≤ 4000		
4000 < WBC > 10,000	4 (26.7)	4 (26.7)
WBC ≥ 10,000		7 (46.7)
Phenobarbiotal (n = 16)[c]		
CPK < 975	3 (18.8)	9 (56.3)
975 ≤ CPK < 10,000		3 (18.8)
WBC ≤ 4000		
4000 < WBC > 10,000	2 (12.5)	5 (31.3)
WBC ≥ 10,000	1 (6.3)	7 (43.8)
Benzodiazepine (n = 30)		
CPK < 975	11 (36.7)	16 (53.3)
975 ≤ CPK < 10,000	1 (3.3)	2 (6.7)
WBC ≤ 4000		
4000 < WBC > 10,000	7 (23.3)	9 (30)
WBC ≥ 10,000	5 (16.7)	9 (30)
Opium (n = 31)		
CPK < 975	8 (25.8)	17 (54.8)
975 ≤ CPK < 10,000	2 (6.5)	4 (12.9)
WBC ≤ 4000	1 (3.2)	1 (3.2)
4000 < WBC > 10,000	2 (6.5)	10 (32.3)
WBC ≥ 10,000	7 (22.6)	10 (32.3)
Acetaminophen (n = 28)		
CPK < 975	7 (25)	18 (64.3)
975 ≤ CPK < 10,000	1 (3.6)	2 (7.1)
WBC ≤ 4000		
4000 < WBC > 10,000	4 (14.3)	10 (35.7)
WBC ≥ 10,000	4 (13.3)	10 (35.7)

[a] Values are expressed as No. (%).
[b] There was not any hypothermia.
[c] There were three reports of temperature ≥ 40°C in the patients poisoned with amphetamine (n = 2) or phenobarbital (n = 1), which are not shown in this table.

In this study, 13.2% of cases met the criteria for rhabdomyolysis (CPK more than five times the normal amount, that is, ≥ 975 IU/L) on the day of their admission to the hospital. In our previous study, 79% of patients suspected to have rhabdomyolysis had a CPK count of more than 975 IU/L, and 65% of them had a fever. In the present study, a fever was reported in73.2% of patients with rhabdomyolysis and 70.6% of patients without it (20). Therefore, rhab-

domyolysis should be considered as a possible cause of fever in these patients. In the current study, around 50% of poisoned patients with rhabdomyolysis had been poisoned with opioid or methadone. This finding is compatible with our previous study, in which we found that the most common cause (23.3%) of rhabdomyolysis was opium. We measured CPK in the first four hours after admission, so the lower finding in this study is not surprising, since in poisoning cases, an increase in CPK occurs in the first 24 hours after exposure to the toxin. This is a limitation of this study.

Of the poisons examined in this study, aluminum phosphate was the most common cause of mortality, and most of the patients who died had a low-grade fever or a normal temperature. This indicates that mortality in patients poisoned with ALP was not related to their high body temperature and that the ALP poisoning was the main cause of mortality. The high prevalence of ALP toxicity in this study is notable. In our previous studies, pesticide toxicity, such as ALP, was reported in just 6.66% of the patients. However, pesticide poisoning was the most common cause of death (24.84%) from 2006 to 2011. In this study, ALP mortality was 8.7%, and more than half of the patients with ALP poisoning died (6, 21).

About 59% of the subjects in this study were male. In other studies, such as those done in Turkey and western Iran, the majority of poisoned patients (71.3% to 59.2%) were female (22, 23). Since poisoning occurs more often in young populations, the mean patient age in our study of 32.65 ± 14.40 is completely predictable. This figure is supported by a study by Zohre E et al. which mentioned that the majority of poisoning victims were younger (22).

Hyperthermia may induce life-threatening complications and is one contributing factor to the development of more severe clinical symptoms mentioned in some literature (24, 25). This study also shows that CNS stimulants, such as amphetamines, can lead to fever, hyperthermia and life-threatening complications.

This study was the first to measure and compare the temperatures of patients poisoned by a variety of toxins, so it provides groundwork for future similar comparative studies. One weakness of the study is that we measured CPK in the first four hours, but CPK increases in poisoning cases over the first 24 hours. Therefore, this study may not accurately or adequately compare CPK levels; however, since CPK rises in poisoned patients, this could also be a strength of the study.

In human poisoning cases, changes in body temperature should be approached with special attention and care. We did not find any controversy over hypothermia in the literature. We did find some patterns of fever and hyperthermia in different types of poisoning. If there are no limits to diagnose fever and hyperthermia, increased body temperature in any case with a poor prognosis that does not respond to treatment could be dismissed as drug-induced hyperthermia. Therefore, a different approach is needed for poisoned patients.

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Footnotes

Authors' Contribution: Haleh Talaie and Simin Dokht Shoaei had the idea and revised the manuscript for intellectual content and collected data, Morteza Hashemian analyzed data, Arezou Mahdavinejad prepared the bibliography and drafted the article, and Naser Mozafari completed, edited and revised the article. All authors read and approved the final manuscript.

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