Original Article

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Epidemiological Survey of Theophylline Poisoning in a Tertiary Poison Center

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Abstract

Objective: Theophylline belongs to the category of bronchodilators and belongs to the family of methylxanthines. The purpose of this study was the epidemiological and clinical investigation of theophylline poisoning in patients admitted to Loghman Hakim Hospital in Tehran.

Methods: This retrospective study reviewed the archived files of hospitalized patients from 2012 to 2022 by developing a questionnaire. All demographic information and results of examinations and laboratory tests were extracted from the file. The collected data were analyzed by SPSS version 25 software.

Results: The age range of the patients was 3 months to 57 years. Out of 34 studied patients, 79.4% were female and 20.6% were male. The most common symptoms of poisoning were vomiting, nausea, sinus tachycardia, hyperglycemia and respiratory alkalosis. The incidence of hyperglycemia was 47.1%. One person had died.

Conclusion: Poisoning with theophylline is uncommon and is mainly caused by self-harm. Except in severe poisonings, death and serious complications have not followed, and they have mostly recovered with supportive and symptomatic treatments.

Keywords: Exposure, Intoxication, Poisoning, Theophylline.

Introduction

Methylxanthines are derivatives of plant alkaloids that include caffeine, theobromine and theophylline, which have common medicinal properties and clinical effects[1.] Theophylline is a bronchodilator drug that has been widely used in the treatment of asthma and obstructive lung diseases[2]. The use of theophylline has decreased due to its narrow therapeutic window and the development of safer drugs[3]. Among the other factors that reduce the use of theophylline is the high rate of death following poisoning with this drug[4].

Methylxanthines inhibit phosphodiesterase enzyme, they are structural analogs of adenosine and pharmacologically act as adenosine antagonists. Studies have shown that they can increase histone deacetylation. All these properties are effective in their bronchodilation effect[5,6]. Clinical manifestations of theophylline poisoning mostly include gastrointestinal, cardiac, and neurological manifestations. Gastrointestinal manifestations include nausea and vomiting, abdominal pain, reflux, and gastrointestinal bleeding. Cardiac manifestations include dysrhythmias, hypotension, and cardiac arrest. Neurological manifestations include: tremors, convulsions, restlessness and headache[7,8].

The purpose of this study was to investigate the prevalence, clinical symptoms, cause of use, effective treatments, age and gender distribution of theophylline poisoning. Considering the low prevalence of this type of poisoning, another aim of this study is to inform the personnel and to provide management by establishing a protocol in the clinics that provide treatment.

Methods

This study was conducted in a cross-sectional and retrospective manner using the archived files of patients admitted to Loghman Hakim Hospital in Tehran during 10 years from 2012 to 2022. In general, 104 cases were investigated. The number of 70 cases that had consumed another substance along with theophylline were excluded from the study. Thirty-four cases were included in the study.

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All demographic information, results of examinations and laboratory tests were extracted from the files.

The collected data were analyzed by SPSS version 25 software. Scattering and population indices were measured.

The approval of the ethics committee for this study was received from the ethics committee of Shahid Beheshti University of Medical Sciences (IR.SBMU.MSP.REC.1401.153).

Results

Gender distribution included 27 cases (79.4%) of women and 7 cases (20.6%) of men. The age range of the patients was 3 months to 57 years. Most cases of poisoning were in the age group of 15-20 years (38.2%) and the average age of the patients was 21 years. The prevalence of intentional poisoning among these patients was 67.6% (23 cases). In 76.5% of cases, the theophylline formulation used was 200 mg tablets. One person had taken 200 mg capsules and 7 people had taken theophylline syrup. Only three people had a history of asthma.

In general, 64.7% had vomiting and 55.9% had nausea. 5 people had hypertension and 5 people had hypotension. 11 people (32.4%) had sinus tachycardia, 3 people had tachypnea, and 2 people had decreased levels of consciousness (Table 1). The average length of hospitalization was 17 hours, the minimum length of hospitalization was 5 hours and the maximum length of hospitalization was 76 hours. Only one person was admitted to the Intensive care units (ICU).

The results of biochemical blood tests showed that the incidence of hyperglycemia was 47.1%, hypocalcemia 8.8%, hypokalemia 29.4%, metabolic acidosis 11.7%, respiratory alkalosis 29.4%, and hypernatremia 5.9%. Two cases of hyponatremia and one case of hypernatremia were observed. One case had thrombocytosis and 4 cases had anemia. The number of 7 patients (20.6%) had increased Creatine phosphokinase (CPK).

All patients received supportive treatment. Sixteen people (47.05%) were treated with multi-dose charcoal, 8 people (23.5%) were treated with single-dose charcoal, 6 people were treated with gastric lavage, and 10 people were treated with other treatments. Only one patient needed dialysis. None of the patients had kidney failure. The death rate was 2.9% (1 case).

Table 1: Clinical presentation and lab Tests of theophylline poisoning in patients.

Symptoms		Frequency	Percent
Gastrointestinal Symptoms	Vomiting	22	64.7
	Nausea	19	55.9
	Negative	8	23.5
	Abdominal Pain	5	14.7
	Diarrhea	4	11.8
	Heartburn	2	5.9
	Gastrointestinal Bleeding	1	2.9
Neurological Symptoms	Negative	23	67.6
	Headache	5	14.7
	Dizziness	5	14.7
	Agitation	1	2.9
	Seizure	1	2.9
	Hallucination	1	2.9
Pupil Status	Mydriasis	4	11.8
	Miosis	2	5.9
Laboratory Tests	Hyperglycemia	16	47.1
	Hypocalcemia	3	8.8
	Hypercalcemia	1	2.9
	Hyponatremia	2	5.9
	Hypernatremia	1	2.9
	Hypokalemia	10	29.4
	Leukocytosis	19	55.9
	Leukocytosis & Anemia	3	8.8
	Anemia	1	2.9

Discussion and conclusion

This study has reported cases of theophylline poisoning over 10 years in Loghman Hakim Hospital in Tehran. This is the largest study population of theophylline poisoning in Iran. Epidemiological studies on exposure to theophylline are scarce. In 2009, the American Association of Poison Control Centers (AAPCC) reported more than 330 calls about people thought to have been poisoned by theophylline. The Theophylline poisoning rate was approximately 0.4% (9). Theophylline is still recognized as the drug of choice for the treatment of neonatal apnea, asthma, and chronic obstructive pulmonary disease. Unfortunately, side effects can be seen even in therapeutic doses[10].

Our study showed that the most common symptoms of poisoning were vomiting, nausea, sinus tachycardia, hyperglycemia and respiratory alkalosis (Table 1). The most common clinical symptoms found in patients admitted to the emergency department of Dokuz Eylül University included hypokalemia, tachycardia, hyperglycemia, nausea, vomiting, and headache[11]. Evidence has shown that theophylline stimulates the catecholamine pathway by inhibiting insulin by epinephrine. Hyperglycemia is a frequent finding in theophylline poisoning[5,12]. Some studies have also reported that hyperglycemia has a high prevalence of poisoning[7,11,13,14]. Shannon et al. reported the age distribution of theophylline poisoning in the range of 3 months to 98 years with a mean age of 34.5 years[13]. Hocaoğlu also reported the age distribution from 1 month to 90 years, with an average of 24.1 years, which was more

in women[11]. In our study, the age range was 3 months to 57 years. The average age was 21 years.

The mortality rate for theophylline toxicity is estimated at 10%[12]. In one study, theophylline mortality was 2.4% of all drug poisonings[15]. The AAPCC reports that 0.35% of all drug-related deaths are due to theophylline9. Another study reported 2 deaths (4.6%) due to theophylline poisoning[11]. In our study, the mortality rate was 2.9% (1 person). We observed that the most frequent cases of intentional exposure (67.6%) were theophylline. Similar findings have been reported in Hocao.lu study[11].

One of the limitations of this study is the incompleteness of the information included in the files, which did not allow a detailed examination of the clinical and laboratory symptoms of the patients. Also, due to the nature of the study, which in most cases was related to the intention of self-harm, it was not possible to directly examine and directly question the patients.

Overdose of theophylline can cause serious signs and symptoms. With the narrow therapeutic range of the drug, toxicity can be observed even at therapeutic doses of theophylline. Clinicians should be aware of the increased risk of theophylline toxicity in children and elderly patients.

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Conflict of Interest: No conflict of interest was declared by the authors.

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