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Original Article

Review

Case Report

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Editorial

Dear Readers,

We present to you the first issue of our journal for 2023. In this issue, we have published 3 research articles, 1 review and 1 case report that we think you will read with pleasure and interest. We hope that your scientific support will continue to increase in 2023. We would like to thank everyone who contributed to our journal for their support and contributions.

Best Regards.

Eurasian Journal of Toxicology Editorial Board

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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.

Informed Consent: N/A.
Conflict of Interest: No conflict of interest was declared by the authors.

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Original Article
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Carbon Monoxide Poisoning: Comparison of Paediatrics and Adult Patients

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Abstract

Background: Carbon monoxide (CO) gas is a tasteless, odorless and colorless gas and causes many poisonings every year. In this study, paediatric and adult CO poisoning cases admitted to our emergency department were reviewed retrospectively.

Materials and Methods: Paediatric and adult patients who applied to the Emergency Department of Mardin Training and Research Hospital between 01 January 2021 and 31 December 2022 due to CO poisoning due to stove usage were included in the study. Patients were compared according to age, gender, month and time of admission to the emergency department, complaints at admission, laboratory test results and discharge status.

Results: 90 patients admitted to the emergency department due to CO poisoning caused by stoves between 2021-2022 were included in the study. While the rate of female patients in the paediatric age group was 53.3%, the rate of female patients in the adult group was 48.9% (p=0.673). When compared according to the complaints of admission to the hospital, the most common complaint in the paediatric age group was nausea-vomiting with 42.2%, while the most common complaint in the adult group was shortness of breath with 26.7%. In both groups, it was determined that the most frequent application was in January with 48.9%. While 15.6% of children were hospitalized, this rate was 4.4% for adults. (p=0.065). While the carboxyhemoglobin (COHb) value at the time of first admission was 18.36±6.60 in the paediatric group, it was 22.03±10.24 in the adult group (p:0.047). In the control blood gas values taken at discharge, COHb level was 2.76±1.83 in children and 5.10±3.02 in adults (p<0.001).

Results: CO poisoning should always be considered in the differential diagnosis of patients who present to the emergency department with nonspecific symptoms during the winter months. It should not be forgotten that children are affected more and recovery is fast.

Keywords: Carbon monoxide, Emergency department, Poisoning.

Introduction

Carbon monoxide (CO) is an odourless, tasteless, colourless, non-irritating gas that is produced by the combustion of hydrocarbons and can cause death. While the concentration of CO in the atmospheric air is mostly below 0.001%, it can be higher in large cities and indoor areas. CO released as a result of poor combustion of fuels can cause poisoning and deaths at a rate of 1-31%[1]. In the United States, an average of 15,000 people a year apply to emergency department due to CO poisoning. In developing countries, including Turkey, most of the poisonings are caused by heating systems. Clinical signs and symptoms of poisoning are non-specific. That is why CO toxicity is often overlooked. Patients usually present with non-specific symptoms such as headache, malaise, and nausea. Loss of consciousness, coma and death can be seen in severe poisonings[2–4]. Suspicion and anamnesis are extremely important in the diagnosis. Diagnosis is even more difficult in the paediatric age group due to the common cold and infantile colic-like symptoms. Diagnosis is made by finding a high carboxyhaemoglobin (COHb) value in blood gas. There are methods such as elimination of exposure and oxygen support, and in severe cases hyperbaric oxygen therapy. In general, most CO poisonings are not fatal. Cases with mild symptoms and no neurological symptoms can be discharged after 4-6 hours of treatment with the recommendation of a control examination[5,6].

While the most common cause of this poisoning in developed countries is suicide, in developing countries the most common cause is heater stoves with improper or inadequate ventilation. This study aims to evaluate and compare the characteristics, clinical and laboratory findings of paediatric and adult patients who applied to the emergency department with heater stove-induced CO poisoning between 2021-2022.

Material And Method

This study is a retrospectively planned study. Ninety patients who applied to the Mardin Training and Research Hospital Emergency Department between 2021-2022 due to CO poisoning were included in the study. Non-stove CO poisonings were not included in the study. Demographic characteristics such as age and gender, admission times,

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symptoms, and findings at the time of admission, and discharge status of the included cases were evaluated. In addition, examinations such as complete blood count parameters, blood gas parameters, troponin, and lactate at the time of admission were examined. The patients were divided into two groups as paediatric and adult patients. Blood gas values at the time of admission and blood gas values at discharge were evaluated according to age. The COHb value in the venous blood taken into a dry heparinised blood gas injector was studied in the blood gas device (GEM 5000 Premier).

Approval for the study was obtained from the Non-Interventional Research Ethics Committee of Mardin Artuklu University (19.04.2023-94154). The study was conducted in accordance with the Declaration of Helsinki.

Statistical analyses are made using IBM-SPSS version 24. Results were expressed as percentages for categorical variables. Continuous variables were conveniently presented as mean±standard deviation. The $\chi 2$ test was used to determine the relationship between categorical variables. Student-t test was used if continuous variables were parametrically distributed. Statistically significant difference level was determined as $p \leq 0.05$.

Results

Ninety patients admitted to the emergency department due to heater stove-induced CO poisoning between 2021-2022 were included in the study. The patients were divided into two equal groups as under 18 years old (paediatric) and over 18 years old (adult). The mean age of the paediatric patients participating in the study was 7.82±5.19, and the mean age of the adult patients was 36.44±13.16 ($p<0.001$). While the number of female patients in the paediatric age group was 24 (53.3%), the number of female patients in the adult group was 22 (48.9%) ($p=0.673$). When compared according to the complaints of admission to the hospital, the most common complaint in the paediatric age group was nausea-vomiting in 19 (42.2%) patients, while the most common complaint in the adult group was dyspnea in 12 (26.7%) patients. Other presenting complaints were headache in 10 (11.1%), dizziness in 8 (8.9%), flu-like symptoms in 6 (6.7%) and altered consciousness in 6 cases (6.7%). Fifteen (16.7%) patients were found to be asymptomatic at presentation. The most frequent hospital admissions in paediatric and adult patients were between 00.01-08:00, and their frequencies were 48.9% and 53.3%, respectively. 31 (34.4%) patients applied between 08.01-16.00, and 13 (14.4%) patients between 16.01-00.00 ($p=0.907$). When the distribution of the cases according to the months was analysed, it was found that the most common CO poisoning was observed in January with 44 (48.9%) patients in both groups. 22 patients were admitted in February, 12 patients in December, 4 patients in March, and 8 patients in April. While 7 of the paediatric patients (15.6%) were hospitalized, only 2 (4.4%) of the adult patients were hospitalized ($p=0.065$). 1 (2.2%) in the paediatric age group and 5 (11.1%) in the adult age group were referred for Hyperbaric Oxygen therapy. 83.3% (n=75) of the patients were discharged (Table 1).

Table 1: Characteristics of patients presenting with carbon monoxide poisoning.

Variables		*Children n:45*	*Adults n:45*	*Patients n:90*	*p value*
Age, mean±SD		7.82± 5.19	36.44± 13.16		<0.001
Gender, n(%)	*Female*	24(53.3)	22(48.9)	46(51.1)	0.673
Arrival complaints, n(%)	*Asymptomatic*	9(20)	6(13.3)	15(16.7)	0.109
	Nausea-vomiting	19(42.2)	11(36.7)	30(33.3)	
	Headache	3(6.7)	7(15.6)	10(11.1)	
	Dizziness	4(8.9)	4(8.9)	8(8.9)	
	Dyspnea	3(6.7)	12(26.7)	15(16.7)	
	Flu-like symptoms	4(8.9)	2(4.4)	6(6.7)	
	Altered consciousness	3(6.7)	3(6.7)	6(6.7)	
Application time, n(%)	*00.01-08.00*	22(48.9)	24(53.3)	46(51.1)	0.907
	08.01-16.00	16(35.6)	15(33.3)	31(34.4)	
	16.01-00.00	7(15.6)	6(13.3)	13(14.4)	
Application month, n(%)	*January*	22(48.9)	22(48.9)	44(48.9)	0.469
	February	9(20)	13(28.9)	22(24.4)	
	March	3(6.7)	1(2.2)	4(4.4)	
	April	3(6.7)	5(11.1)	8(8.9)	
	December	8(17.8)	4(8.9)	12(13.3)	
Discharge, n(%)	*Hospitalization*	7(15.6)	2(4.4)	9(10)	0.065
	Referred for Hyperbaric Oxygen	1(2.2)	5(11.1)	6(6.7)	
	Discharge	37(82.2)	38(84.4)	75(83.3)	

When the first admission blood values of paediatric and adult patients were compared, no significant difference was found in terms of white blood cell, haemoglobin, platelet, pH, pCO^2, lactate and troponin positivity (Table 2). While the COHb value at the time of first admission was 18.36±6.60 in the paediatric group, it was 22.03±10.24 in the adult group ($p=0.047$). In the control blood gas values taken at discharge, COHb level was 2.76±1.83 in paediatric patients and 5.10 ± 3.02 in adult patients ($p<0.001$).

No mortality was observed in the cases followed up in our hospital.

Table 2: Patients' admission and discharge blood values.

Variables	*Children n:45*	*Adults n:45*	*Patients n:90*	*p value*
First admission blood values				
White Blood Cell	11.67± 5.53	10.68± 3.38	11.18± 4.58	0.309
Hemoglobin	13.23± 5.10	13.62± 1.88	13.43± 3.83	0.633
Platelet	297.53± 72.48	284.06± 53.26	290.80± 63.60	0.318
PH	7.36±0.04	7.36±0.05	7.36±0.05	0.916
PCO²	41.05± 6.64	43.52± 5.84	42.29± 6.34	0.064
Laktate	2.66± 1.42	2.28±1.64	2.47±1.54	0.253
COHb	18.36± 6.60	22.03± 10.24	20.20± 8.77	0.047
Troponin positivity n(%)	9(20)	8(17.8)	17(18.9)	0.788
Discharge values				
PH	7.38±0.06	7.37±0.02	7.38±0.05	0.197
PCO²	40.87± 4.48	41.80± 4.97	41.33± 4.72	0.354
Laktate	1.24±0.52	1.04±0.49	1.14±0.51	0.058
COHb	2.76±1.83	5.10±3.02	3.93±2.74	<0.001

Discussion

CO poisoning is among the important health problems seen in developing countries such as our country. CO poisoning occupies an important place among the poisoning cases admitted to emergency department and affects people of all ages[7]. Studies have shown that CO poisoning is more common in females, and it is thought that this may be related to the low erythrocyte count of women[8,9]. In a study in Ankara between 2007 and 2010, 261 CO poisoning cases were evaluated in a tertiary paediatric hospital and it was found that 51.1% of these cases were girls[10]. In another study group, 38 (44.7%) of 85 patients were male, 47 (55.3%) were women[11]. In our study, the number of female patients in the paediatric age group was 53.3%, while the number of female patients in the adult group was 48.9% (p=0.673).

CO poisoning is among the poisonings that cause the most death and is difficult to diagnose because it can mimic many different clinical pictures. All forms of admission are possible, from flu-like symptoms to coma. It can also manifest itself with diarrhoea and colic in paediatric patients[12]. In studies on this subject, it has been stated that the most common causes of admission to the emergency department are headache, nausea, dizziness and altered consciousness[13,14]. In our study, when compared according to the complaints of admission to the hospital, the most common complaint in the paediatric age group was nausea-vomiting with 42.2%, while the most common complaint in the adult group was dyspnea with 26.7%. Other complaints were headache 11.1%, dizziness 8.9%, flu-like symptoms 6.7%, and altered consciousness. On the other hand, 16.7% of the patients had no complaints at the time of admission.

CO poisoning is more common in winter. The most important reason for the increase in this period is the use of stoves for heating. Cases of poisoning continue due to reasons such as unsuitability of the fuels used for heating, insufficient ventilation, lack of timely maintenance of the heater stove, and the lack of sufficient public knowledge on this matter. In our country, CO poisoning increases especially in winter months[7,10,15]. In the study of Akköse et al., the source of poisoning was stated to be heater stoves at a rate of 80% 16. In our study, all of the patients were selected from the patients who applied due to heater stove poisoning. When the distribution of cases according to months was examined, it was found that the most common CO poisoning was observed in January with 48.9% in both the paediatric and adult groups, similar to other studies.

The most frequent admission time to the hospital was between 18.00-24.00 in the study of Keleş et al., between 24.00-06.00 in the study of Besli et al., and between 16.00-24.00 in the study of Uysalol et al.[17–19]. In our study, the most frequent hospital admissions in paediatric and adult patients were between 00.01-08.00 hours, and their frequencies were 48.9% and 53.3%, respectively. 34.4% of the patients applied between 08.01-16.00 and 14.4% between 16.01-00.00 (p=0.907).

Children are more affected by CO poisoning due to their high basal metabolic rate and tissue oxygen demand. Therefore, it is expected that the symptoms of poisoning will appear early. However, since the ventilation number per minute per body mass unit is high, there is a faster recovery and the need for intensive care is lower[20,21]. In a study by Kandiş et al., in which CO poisoning was evaluated in patients over the age of 16, it was observed that 2.7% of the patients were hospitalised in the ward and 2.3% in the intensive care unit[22]. In another study, it was observed that 12.2% of those diagnosed with CO poisoning in the paediatric emergency department were hospitalised in the ward and 0.4% in the intensive care unit[10]. In our study, 15.6% of paediatric patients were hospitalised, while this rate was 4.4% in adult patients (p=0.065). While the COHb value at the time of first admission was 18.36±6.60 in the paediatric group, it was 22.03±10.24 in the adult group (p=0.047). In our study, although the COHb level was lower in children, the rate of being affected and hospitalised was higher. In the control blood gas values taken at discharge, COHb level was 2.76±1.83 in paediatric patients and 5.10±3.02 in adult patients (p<0.001). In our study, control COHb levels taken

at discharge were found to be lower in paediatric group than in the adult group.

Deaths due to carbon monoxide poisoning have been reported. In our country , the number of deaths due to CO poisoning in 2010 was approximately 5 people per ten million[15]. Although the number of deaths in our country is low compared to the number of patients, in our study, there were no deaths due to CO poisoning.

Being a retrospective study and including data from a single center, are the limitations of the study. There are very few studies comparing paediatric and adult patients in terms of CO poisoning. Epidemiological studies with more extensive data on this subject should be conducted.

Conclusion

CO poisoning from heater stoves is an important health problem in developing countries such as Turkey. The incidence of CO poisoning can be reduced by public education on the subject. CO poisoning should always be considered in the differential diagnosis, particularly in patients who apply to the emergency department with non-specific symptoms during the winter months. It should not be forgotten that children are affected more, yet their recovery is fast.

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Original Article

Eurasian Journal of Toxicology

An Analysis of Dog and Cat Bite Cases Attending a Tertiary Care Hospital, Bursa

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Abstract

Objective: The aim of this study was to investigate the epidemiology of dog and cat bite cases in Bursa, Turkey through 2018–2022.

Materials and Methods: A retrospective patient review was carried out. This study was conducted in the department of the Emergency Medicine of Yuksek Ihtisas Training and Research Hospital, Bursa, Turkey. The injury patterns and epidemiologic data of the patients were evaluated. A total of 92 animal bite cases were reviewed.

Results: This study was enrolled 49 men (53.3%) and 43 women (46.7%) with an average age of 37.09± 16.65 years. None of them died as a consequence of animal bite. The findings indicate that a significant correlation was found between the site of injury, the type of wound, antibiotic use, and the species of the biting animals [(p=0.001), (p<0.001), (p<0.001)]. Cats were found as the cause of animal bites in 58.7% of the cases. Of the studied cases, 97.8% had received rabies vaccination four times.

Conclusion: Education programs of society, vaccination of animals and limiting the number of stray dogs are crucial.

Keywords: Animal bite, cat bites, dog bites, emergency medicine, forensic medicine.

Introduction

Animal bite injury is a crucial public health problem, worldwide. Animal bites are a significant cause of morbidity and mortality due to tissue injury, secondary infections and transmission of the zoonotic diseases[1]. Every year 59.000 human rabies deaths occur all over the world[2]. Those deaths were commonly seen in Asia and Africa, exclusively children below 15 years-old[3]. Animal bite injury is also one of the essential forensic medicine topics in terms of its occurrence and consequences. The physicians of Emergency Medicine (EM) must prepare a forensic report besides serving required treatment.

Dog bite injuries were seen in the rate of 12.9 per 10.000 people of all admissions to the department of EM in the USA[4]. Cat bites are often innocent-looking injuries. Unlike dog bites, they are sharp and penetrating. Ischemia due to deep tissue injury and crushing is not seen in wounds caused by cat bite[5]. The bite force especially depends on the body weight, size and skull's morphology of the animal[6]. While the average bite force of canine teeth of a dog was reported as 926 Newton (N), that was 73.3 N for a cat[6]. The goal of the current study was to reveal the demographics and clinical characteristics of the animal bite injury cases in all age groups. It is also aimed at drawing attention to the epidemiologic data, injury patterns, symptoms, and consequences of such cases using regional data.

Materials and Methods

Our study was approved by the Ethics Committee of the Health Sciences University Bursa Yuksek Ihtisas Training and Research Hospital (No:2011-KAEK-25 2023/05-12). A review was made of the cohort of 92 patients who suffered from animal bite injuries and were presented to the department of EM of the tertiary hospital in Bursa city in Turkey, between 26 January, 2019 and 12 July, 2022. The patient information, including the medical status and epidemiological information, with regard to age, sex, type of treatment, status of vaccination, injury patterns, the species of the biting animals, type of wound, locations of the animal bites, and treatment method was obtained by reviewing the medical records of the patients. Superficial skin lesions were also documented.

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IBM SPSS Statistics for Windows, Version 21.0. (IBM Corp. Armonk, NY: USA. Released 2012) software package program was used for statistical analysis. As statistical analysis, in the data evaluation, for numeric variables mean and standard deviation, frequency tables and percentages, minimum and maximum values and median values were presented. Categorical variables are shown as the number of cases and (%). Kolmogorov-Smirnov test was used for the normality distribution of the data. Whether the assumption of homogeneity of variances was met was investigated with Levene's test. The significance of the difference between the groups in terms of continuous numerical variables in which parametric test statistics assumptions were met was evaluated with Student's t test, while the significance of the difference in terms of continuous numerical variables in which parametric test statistics assumptions were not met, was evaluated with Mann Whitney U test. The chi-square and Fisher's exact tests were performed while evaluating the relation among categorical variables. Results were given in the 95% confidence interval and a p-value below 0.05 was accepted as statistically significant.

Results

Ninety-two animal bite injury cases were included in our cohort. No mortality occurred. Basic demographic and injury features of the 92 patients can be found in Table 1. Males were more frequently involved (n=49, 53.3%) (Table 1). The mean age was found to be 37.09± 16.65 years. It was observed that 80 (87.0%) of the patients applied during the covid-19 lockdown. 55 (59.8%) cases were presented from the urban area of the city. Cat bite was observed in 54 of the patients (58.7%), while the most common bite location was the upper extremity (n= 69, 75.0%). While 90 (97.8%) of the patients were vaccinated against rabies, 66 (71.7%) of them were vaccinated against tetanus. None of the patients needed hospitalization. None of the patients had bone fractures, flap-style injury, or vascular injury in the skin. Other clinical demographic information of the patients was given in Table 1.

The statistical relation among the species of the biting animals and other variables were shown in Table 2. In Chi-square / Fisher's exact analysis performed to determine the relationship between patients' gender, bite period, bite location, anatomical localization of the bite, type of wound, antibiotic use, wound care, rabies and tetanus vaccine, and the species of the biting animals, anatomical localization of the bite, respectively, a significant correlation was found between the site of injury, type of wound, antibiotic use, and the species of the biting animals [(p=0.001), (p<0.001), (p<0.001)].

Cat bites were more frequently seen in the upper extremity, while dog bites were more common in the lower extremities, head, neck, face and thorax, abdomen, and back. Our results demonstrate that all lacerations were the result of dog bites and the usage of antibiotic was higher in dog bites (Table 2).

Table 1: The demographic characteristics of the patients.

Age (year) &		37,09± 16,65
Gender #	Male	49 (53.3)
	Female	43 (46,7)
Time#	During the Covid 19 Lockdown	80 (87.0)
	Other times	12 (13.0)
Place#	Urban	55 (59.8)
	Rural	37 (40.2)
The species of the biting animals#	Cat	54 (58.7)
	Dog	38 (41.3)
	Human	0
	Others	0
Region of injury#	Upper extremity	69 (75.0)
	Lower extremity	15 (16.3)
	Head/neck/face	1 (1.1)
	Chest/Abdomen/back	7 (7.6)
	Not specified	0
Type of wound#	Ecchymosis/abrasions/bruising/ break such as scratch or puncture	83 (90.2)
	Laceration	9 (9.8)
	Flap-style injury	0
	Vascular Injury	0
Antibiotics#	No	69 (75.0)
	Yes	23 (25.0)
Surgical treatment method #	Primary repair	91 (98.9)
	Wound care + debridement:	1 (1,1)
	Skin graft	0
	Vascular repair	0
Vaccinated against rabies#	No	2 (2.2)
	Yes	90 (97.8)
Vaccinated against tetanus #	No	26 (28.3)
	Yes	66 (71.7)
Type of treatment #	Outpatient/observation	92 (100)
	Inpatient	0
	Unknown	0
Number of days of hospitalization #	<7	92 (100)
	7 and higher	0
	Unknown	0
Treatment method#	Medical	92 (100)
	Surgical	0
	Unknown	0
Total#		92 (100)

Data given as & mean±standard deviation , # n (%)

Discussion

Animal bites were commonly seen in our country. In the literature, snake bites were evaluated by the researchers besides the domestic animal bite injuries[7].

Table 2: Correlations of the species of the biting animals and other variables

Variables			the species of the biting animals		Total	Chi-squared/ Fisher's exact test
			Dog	Cat		
Gender	Male	n(%)	22 (44.9)	27 (55.1)	49 (100)	p>0,05#
	Female	n(%)	16 (37.2)	27 (62.8)	43 (100)	
Time	Other times	n(%)	4 (33.3)	8 (66.7)	12 (100)	
	During the Covid 19 Lockdown	n(%)	34 (42.5)	46 (57.5)	80 (100)	p>0,05&
Place	Urban	n(%)	25 (45.5)	30 (54.5)	55 (100)	
	Rural	n(%)	13 (35.1)	24 (64.9)	37 (100)	p>0,05&
Region of injury	Upper extremity	n(%)	21 (30.4)	48 (69.6)	69 (100)	
	Lower extremity	n(%)	10 (66.7)	5 (33.3)	15 (100)	*p=0,001&*
	Head/neck/face	n(%)	1(100)	0	1 (100)	
	Chest/Abdomen/back	n(%)	6 (85.7)	1 (14.3)	7 (100)	
Type of wound	Ecchymosis/abrasions/bruising/break such as scratch or puncture	n(%)	29 (34.9)	54 (65.1)	83 (100)	
	Laceration	n(%)	9 (100)	0	9 (100)	*p<0,001&*
Antibiotics	No	n(%)	16 (23.2)	53 (76.8)	69 (100)	
	Yes	n(%)	22 (95.7)	1 (4.3)	23 (100)	*p<0,001&*
Surgical treatment method	Primary repair:	n(%)	38 (41.8)	53 (58.2)	91 (100)	
	Wound care + debridement	n(%)	0	1 (100)	1 (100)	p>0,05&
Vaccinated against rabies	No	n(%)	0	2 (100)	2 (100)	
	Yes	n(%)	38 (42.2)	52 (57.8)	90 (100)	p>0,05&
Vaccinated against tetanus	No	n(%)	7 (26.9)	19 (73.1)	26 (100)	
	Yes	n(%)	31 (47.0)	35 (53.0)	66 (100)	p>0,05&
Total		n(%)	38 (41.3)	54 (58.7)	92 (100)	

Chi-squared test &; Fisher's exact test,

Neither did any patients sustain extremity amputation nor death. A meta-analysis revealed that the number of male victims was higher (14.90 per 1000 patients) compared to female gender (4.55 per 1000 patients)[8].

Our results are in agreement with a paper from Switzerland which investigated human and animal bite injuries. It was reported that none of the patients needed hospitalization9. Another study conducted in Poland reported that, the most of the victims (79.1%) were treated in the hospital without staying a night but after the treatment they were discharged before the end of day[10].

Somewhat similar to our findings a study conducted in Bursa revealed that cat bites were more frequently seen in the upper extremity (79.77%), whereas dog bites were more common in the lower extremities (48.03%), thorax, and abdomen (4.16%)[11]. However, a study evaluating both cat and dog bite injuries in California for 15 years suggested that upper limbs were the most common injury site for both animal attacks[12].

Partly similar to our results (90.2%), a study conducted in Pakistan, indicated that most of the victims suffered from soft tissue damage (95.9%)[13].

As in our study, many researchers stated that most of the victims did not need surgical intervention (89.1%)(91.4%)(89.8%)[14,5,15].

Several authors have already reported that most of the victims (61.4%)(76%)(89.55%)(88%) were city-dwellers[10,16,17,18].

All of the cases who suffered from laceration, and needed antibiotics were the once bitten by a dog. On contrary to our results, a study was conducted in Australia, reported a significant relation between cat-related injury and increased risk of infection[19]. A possible reason for the huge difference between that study and ours was higher numbers of victims in the former study when compared with ours. The cat bites were suggested to be two times more infectious when compared to dog bites[20].

A study suggested a huge numbers of victims (97.1%) receiving a rabies vaccine when compared with our results (97.8%)[21].

Moreover, a statistically significance between lower extremity injuries and dog bite (Table-2). A study which was performed in Kenya, it was found that there was a significant relation between dog bites and head/face injuries[22].

The limitations of the present study of being conducted in a single center, and therefore, the cohort can not be representative of all cases of dog and cat bites in Bursa city. No statistical association was calculated between the period before and during the curfew of the COVID-19 lockdown period due to the low number of achieved medical records of the cases who admitted before the curfew. These are the limits of our study.

Conclusion

Our study revealed that dog bites were more dangerous compared to cat bites. It can be interpreted that the stray animals are not under enough control. We found significant differences in the two cohorts of the species of the biting animals regarding the type of wound and antibiotic use.

In light of our findings we recommend for children and old age groups to avoid close contact with big dogs and be aware of the infectious nature of cat bites. To give education to both children and their parents to have them learn how to behave to a dog or cat. Development of interventional programs, such as reducing the number of stray dogs, vaccination of animals and raising awareness of the society are vital.

Our findings have three implications. First, by means of the single centre study, injuries of dog and cat bites in the same district were compared. Second, injury patterns, social parameters, and epidemiological differences of the animal related injury cases were revealed. Third, regional data of animal bites was collected.

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Review

Eurasian Journal of Toxicology

Systematic Review on Safety of Bisphenol A: from Invention to the Present

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Abstract

Bisphenol a (BPA) is an industrial chemical that use in the production of polycarbonate plastics and epoxy resins. Recently, BPA has been received increased attention because of its high production volume, widespread applications and possible health effects. General population are mainly exposed orally to BPA through consumption of food and water stored in containers with BPA. In contrast, in occupational settings workers are exposed to BPA through inhalation of BPA dust particles. This review discusses the controversial of the current findings according to in vitro, in vivo and epidemiological studies. BPA exposure is associated with multi-organ toxicity including reproductive, developmental, metabolic and cardiovascular disorders. In order to protect the environmental and human health, numerous scientific bodies and regulatory agencies developed to keep the BPA exposure within the safe level. The various adverse health effect of BPA lead to development of alternatives with less harmful effect. However, the safety of the alternatives is not fully verified. To conclude, the current restrictions and limitations on use of BPA has reduced potential exposure and consequently possible health effect. However, still there are several unanswered questions regarding to the exact toxic effects, metabolism and fate of BPA on human and environmental health.

Keywords: Bisphenol A, Industrial chemical, Toxicity, Safe level, Environmental health.

Introduction

2,2-bis (4-hydroxyphenyl) propane widely known by its commercial name, bisphenol A (BPA), was firstly synthetized by Russian chemist Aleksandr P. Dianin in 1891 via acid catalyzed condensation reaction of two phenol molecules with one molecule of acetone[1].

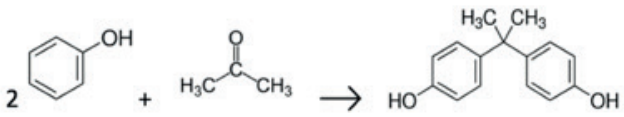

Figure 1: Synthesis of BPA

In 1953, the German scientist discovered that reaction of BPA with phosgene could produce a clear hard resin known as polycarbonate. In mid-twentieth century, BPA was patented under the brand name of "Makrolon" and "Lexan" in Germany and United States, respectively and marketing of BPA as an industrial chemical began[2]. Later on, the commercial production of BPA was rapidly expanded however, it never candidate as a drug and was not suitable as a pharmaceutical. As early as 1934, Edward Charles Dodds, a British biochemist, identified the weak estrogenic properties of BPA while he was looking for a synthetic estrogen by utilizing the rat test systems[3]. In 1993, a team of researcher at Stanford University accidentally found that BPA was leaching from polycarbonate dishes into flask content which interfered their experiment by estrogenic like activity with cells in culture[4]. BPA serves as a main ingredient of polycarbonate polymers and epoxy resins. Polycarbonate has high durability in a wide temperature ranges (-20 °C to 140°C) and resistance to many acids, oxidizing and reducing agents. Transparency and hardness of polycarbonate makes it ideal alternative to glass. In addition, polycarbonate is incredibly useful hard plastic with wide varieties of usage such as compact discs, food container, baby bottles, re-usable water bottles and medical equipment[5]. As polycarbonate, epoxy resins have wide range of consumer and industrial applications due to their toughness, robustness, resistance and adhesion properties. Epoxy resins are used as an inner coating on metal food and beverage containers as well as jar caps to protect food products from direct contact with metal[6]. This protective layer also minimizes the corrasion and leakage of any metal traces that could lead to possible

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food-borne poisoning. In lesser extent, BPA is also used as photoactive dyes in the manufacturing of thermal paper that used in cash receipts. In 2010, a case-control study showed that urinary concentration of conjugated and unconjugated forms of BPA were significantly higher in cashier who had frequent contact with thermal paper by dermal exposure than control group[7]. BPA is one of the best-selling chemicals in the world, with total annual production of 7,082 metric tons in 2022 and is expected to reach 12,169 metric tons by 2032 as reported by total addressable market[8]. The release and distribution of BPA in the natural environment is widespread. Based on biomonitoring data, the human exposure to BPA is nearly ubiquitous. General population are mainly exposed to BPA through direct contact with materials containing BPA and consumption of contaminated food and water. It has been thought that BPA could be released from plastic materials over time and leaching is increased by the aging of material, alkaline condition and heating. BPA as a form of bisphenol A-glycidyl methacrylate is frequently used in dental composites, dental sealants and dental cement. Dental treatment is one of the sources of BPA exposure however the amount of BPA released from dental sealants is far below safe intake limits that set by government bodies. In 2015, European Food Safety Authority (EFSA) estimated the contribution from dental material is limited to 0.001% compared to total BPA exposure from all sources and potential adverse health effect is most likely negligible. Even though, chronic exposure to BPA released from dental material is still a concern[9].

Pharmacokınetıcs of BPA in Human

The absorption, distribution, metabolism and excretion of BPA have been investigated previously. The primary sources of BPA absorption are through ingestion, inhalation, maternofetal transmission and lesser extent through skin contact. Orally introduced BPA rapidly are absorbed through gastrointestinal tract and then metabolized by liver and intestine before reaching the target tissues including testes, fetus or uterus. Due to the presence of hydroxyl group, BPA is metabolized by phase II enzymes via glucuronidation and coupled by uridine 5'diphospho-glucuronosyltransferase (UGT) to BPA mono-glucuronide. Consequently, this biologically inactivated metabolite is excreted from hepatocytes into urine or feces within 24 hours after administration. Several laboratory animal experiments and epidemiological studies confirmed that BPA mono-glucuronide is the major metabolite in the plasma with lack of estrogenic like activity that is known as BPA detoxification process. Any abnormalities in functioning of glucuronosyltransferases enzymes lead to the elevation of unconjugated BPA concentration in the body. At higher doses of BPA treatment, the glucuronidation pathway becomes saturated and other metabolic pathways become activate10. The lesser extent, free BPA is metabolized through sulfotransferase (SULT) metabolizing enzyme. The sulfate conjugates, primarily BPA-sulfate, is minor metabolite that is considered biologically inactive and eliminated from body into the urine via glomerular filtration. 4-Methyl-2,4-bis(4-hydroxyphenyl) pent-1-ene (MBP) is a major active metabolite of BPA that possesses more potent estrogenic activity that BPA11. This metabolite is formed during direct hydroxylation of BPA ring by catalytic activity of microsomal enzymes. In 2011, a study has been found that cytochromes P450 (CYP) enzymes, mainly *CYP3A4* and *CYP3A5*, in the liver had ability to mediate the metabolism of BPA into isopropenyl phenyl (IPP) and hydroxycumul alcohol (HAC). Both metabolites are originated from carbocation intermediate and have high estrogen receptor binding properties[12].

BPA in both free and conjugated form could excreted in urine with a half-life of approximately 6 hours. Therefore, the urinary concentration of total BPA reflects recent, mostly within 24 h, exposure to the BPA. However, free form of BPA is biologically active and lipophilic in nature that has ability to accumulate in different human and animal compartments especially adipose tissue[10]. Various biological samples could be used for the biomonitoring of BPA, including blood, urine, amniotic fluid, hair and other tissues. Human biomonitoring studies have reported BPA can pass through placenta and influence fetal growth in uterus[13].

Toxicological Aspect of BPA

In 2017, the Member State of the European Chemicals Agency (ECHA) was classified BPA as a Substance of Very High Concern (SVHC) under category 1B, due to being toxic for reproduction and endocrine disruptor for both the human health and ecosystem14. BPA is considered to have an estrogenic-like and anti-androgenic properties that resulting in harmful impact on different systems and organs including

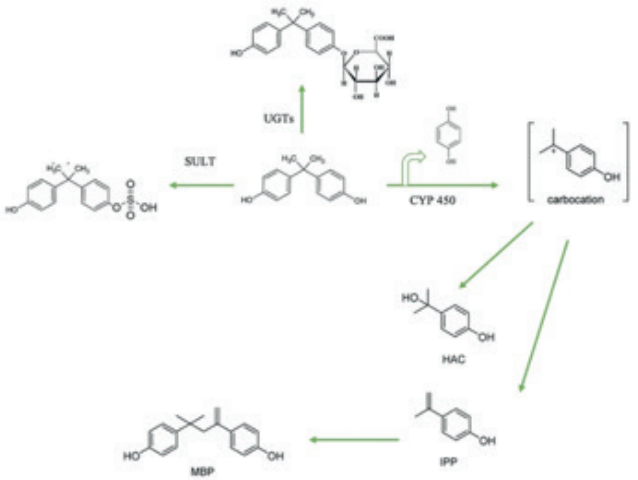

Figure 2: BPA and its four metabolites

developmental system, reproductive system immune system and metabolic disorders.

Reproductive System

Several studies documenting that BPA downregulates the activity of sex hormones and increases the incidence of infertility in both men and women. BPA is mimic estrogen hormone and binds to estrogen-related receptors such as ERα and ERβ, androgen receptors and aryl hydrocarbon receptors therefore interrupts activity and balance of sex hormones. The primary effects are elevated the concentration of hormones like progesterone, estradiol and luteinizing hormone and decreasing the concentration of cortisol[15]. It has been claimed that alterations of endometrial structure are associated with perturbation of sex hormone. Changes in ovarian morphology and ovulation as a result of BPA exposure have been well documented. Several studies have found aged-based relationship between BPA levels and changes of endometrial wall thickness. Scientists have found that exposure to BPA results in endometrial wall thickness in women less than 37 years old while women older than 37 years had a negative correlation with urinary BPA levels and thickness of endometrial wall[16]. BPA is also associated with increased incidence of cystic endometrial hyperplasia, stromal polyps, atypical hyperplasia and pregnancy problems such as miscarriage[17]. Experimental studies suggested a negative association between urinary BPA concentration and male reproductive system including decrease spermatogenesis, sperm motility, viability and abnormal sperm morphology ultimately decreasing male fertility and reproductive potential18. A study at reproductive center in Taiyuan evaluated the effect of chronic exposure to BPA on male sexual function. Among the participants, the primary effects were sexual dysfunction, reduced levels of libido following by reduced erection ability, reduced ejaculation intensity and premature ejaculation[19].

Developmental Systems

Accumulating evidence suggests that prenatal exposure to BPA altered the brain growth and behavior neural development such as hyperactivity disorder, depression, anxiety, prosocial behavior, learning-memory impairment and language development[20]. In addition to the change in growth and development of offspring during prenatal exposure, BPA exposure also cause precocious puberty in both girls and boys during the pubertal period. The underlying mechanisms of precocious puberty and premature thelarche caused by BPA exposure is related to its xeno-estrogenic activity[21]. Many studies have proven that BPA can disrupt hypothalamic-pituitary-gonadal axis causing to increase the concentration of gonadotropin releasing hormone and follicle stimulating hormone. A study in 2018 showed that, prenatal exposure to BPA might increase serum GnRH level and induced abnormal estrus cycle[22]. An occupational cohort study in China has proved a dose-response relationship between increased maternal exposure to BPA during pregnancy and greater magnitude of shortened anogenital distance (AGD) in male offspring[23]. A pregnancy cohort study concluded that, BPA concentration in first trimester maternal urine was associated with shortened AGD in newborn female. This study hypothesis that, BPA exposure during pregnancy alters typical gestational endocrine signaling pathway through estrogen receptor agonistic activity[24].

BPA Induced Metabolic Disorders

Several epidemiological data suggest that BPA negatively impacts on metabolic homeostasis. The relationship between urinary BPA concentration and risk of metabolic syndrome, diabetic mellitus and obesity development were extensively studied. One possible mechanism is mitochondrial dysfunction through increasing oxidative mediators and decreasing antioxidative enzymes. Besides that, BPA has been shown to alter synthesis and release of insulin by pancreatic B-cells and induces insulin resistance25. In 2010, Alonso-Magdalena et. al. have found that BPA exposure results to metabolic disorder through disrupting the glucose homoeostasis on animal model. The result showed that offspring had lower glucose tolerance, higher insulin resistance and higher plasma level of insulin, leptin, triglycerides and glycerol compare to control group26. Epidemiological studies and laboratory experiments showed that higher concentrations of BPA in urine were correlated with higher incidence of cardiovascular toxicity including peripheral arterial disease, coronary heart disease and higher blood pressure during pregnancy. Prenatal BPA exposure was reported to lead to multiple cardiac disorders in a sex specific manner. In female model BPA suppressed the migration of endothelial progenitor cells and high systolic blood pressure through mediate estrogen receptor α. In male model impaired vascular vasoresponsiveness and reduced cardiac remodeling were observed as well[27].

Other Health Effects Linked to BPA

In the study of Linillos-Pradillo et. al. the higher BPA concentration were associated with increased aspartate aminotransferase and alanine aminotransferase level in rat model compare to control group. This study concluded that both low and high dose of BPA can cause hepatic trauma through induces oxidative stress, mitochondria mediated apoptosis, genomic damage and alteration in liver enzyme levels[28]. In 2017 Kobroob et. al. found that BPA had negative impact on the kidney and leaded to deterioration of renal function including glomerular filtration and tubular function. BPA exposure resulted in azotemia, as indicated by increases in blood urea nitrogen and serum creatinine level[29]. In vivo and in vitro studies have suggested BPA with potential carcinogenic functions. BPA exposure

can significantly impact growth, proliferation, migration and apoptosis of cancer cells. Although, possible pro-carcinogenic effect of BPA is suggested by many studies, still there is inadequate epidemiological evidence to consider BPA as a human carcinogen and international agency for research on cancer (IARC) has not yet classified BPA as to its potential carcinogenicity30. Also, several published studies suggested that BPA could disrupt the normal respiratory function, immune function and increase risk of some neurodevelopmental diseases[15].

Safe Level of BPA Exposure

Due to the controversy over safety of BPA, numerous scientific studies and regulatory bodies expanded to assessed hazards and risk as result of dietary and non-dietary exposure to BPA. In 2002, the International Program for Chemical Safety (IPCS) of the World Health Organization (WHO) published that many endocrine disrupting chemicals such as BPA were not following common dose response rules[31]. Several mechanisms are involved in this phenomenon. The receptors may be stimulated by low doses and inhibited by overdoses because receptor-mediated responses saturate. In 2012, the National Institute of Environmental Health Science together with the National Toxicology Program (NTP) and Food and Drug Administration (FDA) developed the Consortium Linking Academic and Regulatory Insight on BPA toxicity (CLARITY-BPA). This program as name of CLARITY performed a regulatory-style study to assess the full range of potential health effects by using identical animal strains and experimental conditions to resolve uncertainties on BPA toxicity[22]. A recent study as a part of CLARITY-BPA addressed that BPA produce an unconventional dose-response curve typically known as non-monotonic dose response curve. BPA changed the believe that high doses produce more serious effects than low ones. A study assessed the dose response of BPA on female rat cardiac myocytes via evaluating multiple end points including development of arrhythmic activities, myocyte mechanics and calcium transient[32]. The result was in agreement with previous studies that low dose BPA rapidly stimulated the contraction of female myocytes while the effect declined at the higher concentration. The European Commission (EC) includes BPA in the list of chemicals in terms of its application in manufacturing of plastic materials that indented to come into contact with food. However, only a limited amount is allowed to leach from the material into food that known as specific migration limit (SML)[33]. In 2002, the EC established SML for BPA at 3 mg/kg of foodstuff and later on, EC re-evaluate the risks and introduced stricter limits on BPA in food contact materials, therefore, decreased the SML to 0.05 mg/kg of food on 2018[34]. Since 2011, different measures have been taken to limit population exposure to BPA. Infants and toddlers are more susceptible to hazardous chemicals such as BPA due to physiological differences, immature immune system and insufficient detoxification system. Infancy is the key period for mental and physical development and BPA could adversely affect the behavior, brain and prostate gland in fetus, infant and young children. Therefore, in 2012 the FDA banned the use of BPA in baby bottles and sippy cups. This change was followed in 2013 to disallow the use of BPA-based epoxy resins as a coating in packaging for infant formula[35]. Panel of food contact material and Enzymes and Processing Aids (CEP Panel) suggested the safe exposure limit, known as tolerable daily intake (TDI), for industrial chemicals such as BPA. This limit refers to the amount of a substance in air, food or drinking water that can be taken daily over a lifetime without appreciable health risk. In 2006, EFSA set an identical TDI for BPA at 50 µg/kg body weight/day based on available toxicological data. This value was calculated by diving no observed adverse effect level (NOAEL) of 5 mg/kg body weight /day that derived from animal experiment by a safety factor of 100 to account for interspecies variability of 10 and intraspecies variability of 10[36].

$$\text{ADI (human dose)} = \frac{\text{NOAEL (experimental dose)}}{\text{Safety Factor (100)}}$$

Figure 3: The equation uses to calculate ADI of BPA

The EFSA provided the risk assessment analysis based on identified two multi-generation reproductive toxicity studies in rodents. The effect of BPA on body and organ weight in adult and offspring rats as well as liver function in adult mice were observed. This study confirmed that a dose of 5 mg/kg b.w. of BPA was without any adverse effect on mice and their offspring. In 2015, EFSA performed new hazard characterization of BPA based on potential health effects, exposure estimates and evaluation the risks for human health37. EFSA lowered the TDI of BPA from 50 to 4 µg/kg body weight/day. This was based on applying a safety factor of 150 to the NOAEL of 609 µg/kg body weight/day. Several studies during the 2013 to 2018 revealed that BPA could adversely affect the immune system particularly via increasing in the proportion of certain cells called T-helper cells in mice. Eventually, in 2021, EFSA proposed to reduce the TDI 100 000 times lower to 0.04 ng/kg body weight /day. The current TDI value is safe and this value does not pose health risk to consumer therefore other that infant products, BPA below this level is eligible to be use as a part of food contact material[38].

Occupational Exposure to BPA

As the production and consumption of BPA is increasing, consequently the number of individuals that are occupationally exposed to this compound is increased dramatically. Therefore, there is an urgent need to understanding, characterizing and quantifying the workers

exposure to BPA in different occupational setting to provide a preventive and protective measures in work place. Threshold Limit Value (TLV) and Permissible Exposure Limits (PEL) are legal limits that referring to airborne concentrations of chemical substances and conditions where nearly all workers may be repeatedly exposed over a working lifetime without developing any adverse effects. In order to protect the workers and minimize worker's exposure to hazardous concentration. PEL is regulated by Occupation Safety and Health Administration (OSHA) whereas TLV set by American Conference of Governmental Industrial Hygienists (ACGIH)[39]. Yet there is neither specific TLV nor PEL for BPA in working place. However, the OSHA and ACGIH established an exposure limit for total dust that workers may be contact at 15 mg/m3 and 10 mg/m3 respectively40. Additionally, Europe has been established specific exposure limits for BPA at 3 mg/m3. Biological monitoring provides an important role to assess exposure and health risk to works in occupational settings. In 2013-2014, the National Institute for Occupational Safety and Health (NIOSH) conducted a biomonitoring study to examine the exposure of BPA at six US companies that are BPA manufacturers or make BPA-based materials. Over two consecutive days, series of urine samples of 77 workers were collected and analyzed. The result had shown that workers in the NIOSH study had BPA levels in their urine 70 times higher than general population in the U.S. However, more than 99% of detected BPA in urine was in conjugated form that were biologically inactivate. Unlike general populations, workers in this study were mainly exposed to BPA repeatedly through inhalation or dermal contact[41].

Alternatives to BPA

As mentioned above, the use of BPA in baby bottles were banded by Canada in 2008, in France in 2010 and in EU in 2011[42]. Such regulations and public health concerns has led to the removal of BPA from many commercial products and development of substitutes. Bisphenol S (BPS) and bisphenol F (BPF) are the most common alternatives of BPA that are used in the manufacturing of several consumer products including hard plastic items, food packaging and container as well as household products. These two analogs share close chemical structural similarities with BPA[43].

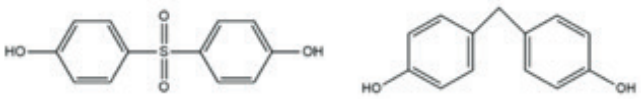

Figure 4: Chemical structure of BPS (left) and BPF (right)

The BPA replacement products are marketed under the labelled of "BPA free". In 2016, the use of BPA was restricted in thermal paper and by 2022, 61% of all thermal paper in the EU was replaced by BPS[44]. It is hypothesized that BPA alternatives are less likely to leach into food and beverage products and more resistant to heat. Although BPS and BPF are thought as safer alternatives to BPA, recent in vitro and in vivo studies revealed the anti-androgenic and estrogenic activities of these compounds in cell lines of different species. The safety and health risk of BPS is controversial. Some toxicological studies have concluded that BPS exposure impairs endocrine system as well as increases incidence of obesity and thyroid hormones[45]. For the first time in 2019, a study was designed to evaluate the maternofetal placental transfer rate of BPS and its main metabolite, BPS glucuronide, by using the human placental perfusion model. The results show that despite the structural similarities of bisphenols, BPS is a polar molecule with low lipid solubility therefore has lower rate of placenta diffusion compare to BPA. This study concluded that the blood placental barrier preventing fetus exposure to BPS and its metabolite[46]. In 2021, a study conducted by Kaptaner et. al., was showed that BPS exposure induced hepatocyte toxicity in rainbow trout fish via decreasing the activity of free radical scavenging enzymes including superoxide dismutase, glutathione and catalase as well as increasing oxidative stress and lipid peroxidation[47]. In contrast in 2021, Castellini et al. designed a study to investigate in vitro effect of BPS and BPF on human spermatozoa. This study concluded that BPS and BPF alone or in combination form had neutral effect on sperm viability, motility as well as sperm mitochondrial function. The results showed that these two analogs seem to be safer alternative to BPA for sperm biology48. However, information regarding to the biological activities of these two alternatives are still limited and toxicity as well as potential adverse effects for human health is not clear yet. To conclude, the utilization of BPS and BPF instead of BPA as safe alternative in consumer products should be carried out with caution and awareness.

Conclusion and Perspective

BPA has been received increased attention because of widespread usage, ubiquitous human exposure and possible health effect. Several studies showed estrogenic and antiandrogenic effect of BPA and target different organs. Regulatory agencies (FDA and EFSA) provide broad risk assessments to identify hazard associated with BPA exposure over years and extensively reviewed the available toxicological data to decide the safest level for BPA. EFSA has lowered the estimated safe level of BPA in order to minimize the possible risks to public health. Even though the level of BPA exposure is far below the established safe level, some precautionary measures should be taken to minimize the adverse health effect. These including limit the use of canned foods, avoid heat to plastic material, switch to BPA-free products and development of safer alternative to BPA. Figure 5 highlighted the scientific finding and major limitation of BPA from invention to the present. Although BPS and BPF are alternatives to BPA, they are not innocent

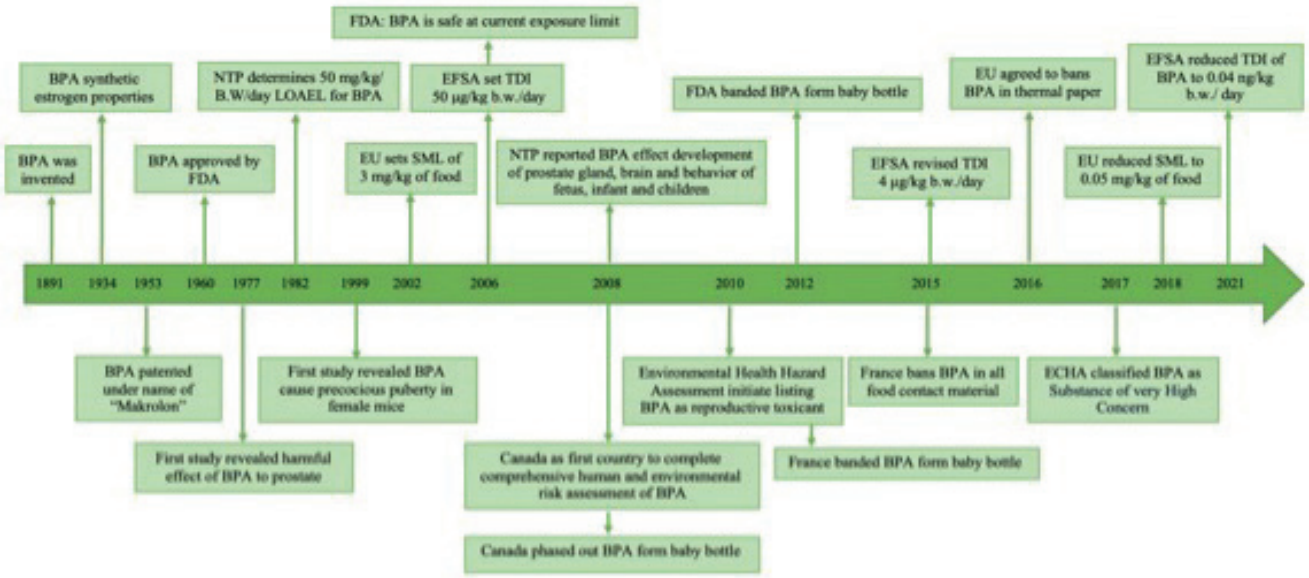

Figure 5: A timeline of the major scientific findings and limitations of BPA from invention to the present.
*NTP: national toxicology program, EU: European union, SML: specific migration limit, EFSA: European food safety authority, TDI: therapeutic daily intake, FDA: food and drug administration, ECHA: European chemicals agency

enough in terms of toxicity, but they are currently the only available alternatives to BPA. This work brings to light the need for further risk assessments, development of better alternatives, BPA free products and greater public awareness.

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Case Report
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Two Patients of 113 and 77 Years Old of Atropa Belladonna Poisoning Case Report

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Abstract

Atropa belladonna is a deadly poisonous plant. Its roots, leaves and fruits contain alkaloids: atropine, hyosciamine and scopolamine. Atropa belladonna poisoning is a serious condition and should be considered in the presence of anticholinergic toxidroma. Treatment is mainly symptomatic, including gastrointestinal decontamination with activated charcoal. In severe cases, physostigmine can be used as an antidote. Atropa Belladonna poisoning should be considered in a patient with symptoms of anticholinergic poisoning.

Keywords: Atropa belladonna, Poisoning, Emergency medicine.

Introduction

Atropa Belladonna is a poisonous plant species in the solanaceae family[1]. It grows wild in our provinces such as the Black Sea Region, Kırklareli, Bolu, Balıkesir, Adana, Hatay and Osmaniye[2]. Among the people, it is also known by names such as beautiful horseradish, bell pepper, nightshade, death bell, bear strawberry, wolfberry, yidin, black grape, devil cherry/cherry, and wild tobacco[2]. The poisonous components of this plant are substances called alkaloids. The most important substances that make up the total alkaloid are; hyoscyamine, atropine, scololamine, apoatropine, simetropium and belladonnin[3, 4]. However, the essential substance is Atropine, constituting 95% of the total alkaloid[5]. Atropa Belladonna poisoning occurs as a result of consumption, inhalation, or skin contact of this plant and can be potentially life-threatening. Atropa Belladonna causes poisoning with its anticholinergic effect. Anticholinergic toxic syndrome (ATS) affects the central and peripheral nervous systems together and presents with findings such as delirium, hallucinations, tachycardia, choreoathetoid movements, mydriasis, and dry skin[1, 5, 6].

Case Report

Two female patients, one 113 years old and the other 77 years old, presented to the emergency department with complaints of tachycardia, dry skin, mydriasis, confusion, abnormal arm movements and speech disorder. The patients and their relatives stated that they used some of the plants grown in their gardens while cooking. It was learned that the same complaints started in both patients after eating the plant. When they brought the plant they used, it was understood that the plant was atropa belladonna, which is known among the people as beautiful herb and has an anticholinergic effect. Atropa Belladonna poisoning was considered due to the presence of anticholinergic symptoms/findings in the patients and the history of ingestion of belladonna.

Both patients had only hypertension in their history. On physical examination, patients had pale skin and rapid breathing. Eye examinations revealed mydriasis and decreased light reflex. The patients expressed symptoms such as dryness of the skin, redness and burning sensation in the mouth, which are signs of anticholinergic effects. In the examination of the patients, choreoathetoid movements

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(uncontrollable abnormal arm movements) were also detected. The blood pressure of the patients was measured at normal values (130/90 mmHg, 135/95 mmHg). Pulse rates were tachycardic (110/minute, 105/minute). Their body temperature increased to 38 C°. No emergency pathology was detected in the brain tomography and diffusion MR imaging of the patients. No pathology was detected in the laboratory tests of the patients. Sinus tachycardia was detected in ECGs. The patients were diagnosed with Atropa Belladonna poisoning and emergency treatment was initiated. Patients were decontaminated with activated charcoal, intravenous fluid replacement was provided, and peripheral cooling was applied. The use of physostigmine was considered to reverse the anticholinergic effects, but since physostigmine was not available, symptomatic supportive treatment, peripheral cooling, close hemodynamic monitoring, neurological and vital signs monitoring, airway patency/maintenance, respiratory and circulatory support (hydration) and conservative treatment were used and benzodiazepine was administered for agitation. During this period, patients were admitted to the ward. During hospitalization and treatment, the symptoms and findings of the patients improved. The patients were discharged with recovery.

Discussion

Kati et al. in his study, it was stated that the most common causes of acute poisoning in geriatric patients were drug poisoning in 54%, carbon monoxide poisoning in 27%, pesticide poisoning in 12.7%, food (plant) poisoning in 4.8% and corrosive substance poisoning in 1.6% [7].

Since impaired consciousness, which can be seen in geriatric poisoning cases, can be confused with acute cerebrovascular events, taking a detailed anamnesis as well as clinical examination and imaging methods will be life-saving. Especially in geriatric patients presenting with clouding of consciousness, hallucinations, meaningless body movements and speech findings, poisoning due to plants should be considered in the differential diagnosis[1].

Atropa belladonna poisoning is a rare but potentially life-threatening condition[8]. This poisoning is usually caused by accidentally consuming the plant as a result of not recognizing the plant. This case report is important for understanding the symptoms and treatment approaches associated with Atropa Belladonna poisoning. The plant Atropa Belladonna contains poisonous compounds called tropane alkaloids. These compounds may cause various symptoms by affecting the central nervous system and cardiovascular system due to their anticholinergic effects[5, 6, 9]. As seen in the case report, symptoms such as clouding of consciousness, tachycardia, mydriasis and dry mouth/skin appeared in the patients. These symptoms are characteristic signs of Atropa Belladonna poisoning. The diagnosis is supported by the patient's history, physical examination findings, and laboratory tests. Treatment should begin quickly. Bowel sounds should be checked before administration of activated charcoal because of the risk of ileus. Activated charcoal can be used for decontamination and intravenous (IV) fluid replacement should be provided[1, 5, 6, 9]. The antidote of anticholinergic toxidromes (poisonings) is Physostigmine[10]. As a general approach, it is used in cases where the patient's clinical condition cannot be controlled (such as hyperthermia, delirium or tachycardia) together with physostigmine, benzodiazepine administration and hydration. Physostigmine dose; It is administered as 0.5-2 mg IV (administered in 5 minutes) in adults and 20 µg / kg (0.02 mg / kg) in children[1, 5, 6].

When we examine the emergency and supportive measures in the treatment of Atropa Belladonna poisoning in the literature; The first stage is stabilization of the airway, respiratory system, circulatory system and vital signs. If the patient is agitated, hallucinating, and has seizures, benzodiazepines can be used for supportive treatment. If hyperthermia is detected, peripheral cooling methods, antipyretic agents and benzodiazepines can be used. Urinary retention may develop in the patient presenting with anticholinergic toxidroma. If urinary retention is detected in patients, a Foley catheter should be inserted. Rhabdomyolysis can be seen in patients and attention should be paid[1, 5, 6].

Conclusion

Atropa Belladonna poisoning is a condition that can have serious consequences. Atropa Belladonna poisoning may cause anticholinergic effects on the central nervous system and cardiovascular system. Early diagnosis and appropriate treatment are important to protect the health of patients. It is vital for healthcare professionals to have knowledge about the symptoms, signs, diagnosis, treatment and prognosis of poisonings and to be able to define them accurately. Raising awareness of the public about recognizing and not consuming poisonous plants will help prevent such poisoning cases. Awareness of health workers and the public on this issue will contribute to reducing poisoning cases and achieving better results.

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