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Demographic and Clinical Characteristics of Theophylline Exposures between 1993 and 2011

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Background: Acute and chronic exposure to theophylline can cause serious signs and symptoms of poisoning. Additionally, with a narrow therapeutic range, toxicity could be observed even with therapeutic doses of theophylline. Epidemiological data on theophylline exposures in our country are extremely limited. The results of our study may improve the clinical management of theophylline poisoning in our country and elsewhere.

Aims: To present aetiological and demographic features, clinical findings and treatment attempts with regard to theophylline exposures reported to Dokuz Eylül University Drug and Poison Information Center (DPIC), between 1993 and 2011.

Study Design: Descriptive study.

Methods: The data regarding demographics, date, time, type of exposure, route of and reason for exposure, signs and symptoms upon admission, clinical management and outcome were retrospectively evaluated.

Results: The DPIC recorded 88,562 poisoning calls between 1993 and 2011; 354 (0.4%) of them were due to theophylline exposure. The mean age of all cases was 24.1±15.4 (range between 1 month and 90 years). Females dominated all age groups (72.6%, 257 females). Intentional exposure was significantly higher in women than in men (88.2% vs. 68.2% for all age groups; $p<0.001$ for children; $p<0.001$ for adults; $p<0.001$ for all age groups). While 60.5% of the cases had no symptoms, severe signs of toxicity were present in 1.9% of theophylline exposure cases during the telephone inquiry. Signs and symptoms were found to be significantly more prevalent in adults than in children ($p<0.01$). The serum theophylline level was regarded as toxic in 74% (65 toxic levels) of theophylline measured cases. Clinical signs and symptoms were found to be significantly prevalent in cases with toxic theophylline levels ($p<0.001$). The rate of gastrointestinal decontamination procedures was higher than that of recommended gastrointestinal decontamination procedures by DPIC (83% and 66%, respectively). There were two fatalities (4.6%) associated with chronic theophylline toxicity and theophylline overdose in an acute setting for suicide (a 90 year-old and 25 year-old, respectively).

Conclusion: Although most of the theophylline exposure cases had no symptoms, some reported serious signs and symptoms of poisoning such as hypokalaemia, tachycardia and hyperglycaemia. DPICs have an important role in the management of theophylline exposure without unnecessary gastrointestinal decontamination procedures.

Key Words: Exposure, Drug and Poison Information Center, poisoning, retrospective, theophylline

Theophylline, a member of the xanthine family, has been used in the treatment of asthma, chronic obstructive pulmonary disease and apnoea (1, 2). Because of the narrow therapeutic index of theophylline, therapeutic drug monitoring is indicated for safe and effective treatment (3). Clinical manifestations of theophylline toxicity include nausea, vomiting, hypokalaemia, hyperglycaemia, metabolic acidosis, tachycardia, cardiac arrhythmias, and seizures (3, 4). Although its clinical use has decreased remarkably because safer and more effective drugs have been introduced, theophylline use continues to result in potentially life-threatening toxicity (1, 4).

The aim of this study was to investigate aetiological, demographic and clinical characteristics of the patients with theophylline exposure reported to the Dokuz Eylül University Drug and Poison Information Center (DPIC), in Turkey, in a 19-year period. There is no comprehensive descriptive research study available concerning theophylline toxicity in Turkey. The results of our study may therefore improve clini-

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cal management of theophylline poisoning in our country and elsewhere.

MATERIALS AND METHODS

This study was approved by the Institutional Ethics Committee of Dokuz Eylül University (Protocol number: 716-GOA/2012).

A cross-sectional, descriptive review was conducted for cases with theophylline exposure between 1993 and 2011 reported to Dokuz Eylül University Drug and Poison Information Center (DPIC), which provides consultation via telephone, mainly to the hospitals in the Aegean Region of Turkey, including Dokuz Eylül University Hospital. The number of cases reported to the DPIC was approximately 4,500 per year. Data were obtained from DPIC and Dokuz Eylül University Hospital archives and analysed for demographics, exposure time and date, type of exposure (acute, chronic or acute-on-chronic; intentional or unintentional), route of administration, signs and symptoms upon admission, serum theophylline level, presence of co-administered drugs, clinical management, length of hospital stay, and outcome. A broader range of data for patients admitted to Dokuz Eylül University Hospital was accessible for analysis, whereas data were restricted for patients admitted to other centres.

Ages of patients were categorised as 0 to 17 for children, and 18 and above for adults; children were further divided into two age groups: 0-6 years and 7-18 years. The severity of clinical manifestations was graded as asymptomatic, mild, moderate or severe according to the European Association of Poison Centers and Clinical Toxicologists, International Program on Chemical Safety Poisoning Severity Score (5). The therapeutic range of serum theophylline concentration was defined as 10 to 20 mg/mL. Serum theophylline levels lower than 10 mg/mL and higher than 20 mg/mL were defined as sub-therapeutic and toxic levels, respectively (3). Results were presented as mean±SEM and percentage (%). Results were considered statistically significant when $p<0.05$. A new software package named "Ruber" (İzmir, Turkey), which was developed for poison information centres with guidance from the DPIC, and the Statistical Package for Social Sciences for Windows 15.0 (SPSS) were used for statistical analysis. Descriptive statistics, contingency tables and Pearson Chi-square test were performed to analyse the data.

RESULTS

Demographics and clinical characteristics

Between 1993 and 2011, 88,562 poison exposure cases were reported to Dokuz Eylul University Drug and Poison Information Center (DPIC) with theophylline being the causative agent in 0.4% (354). Of these cases, 97.7% were reported by hospitals and other healthcare facilities and 11.6% (41) were reported by Dokuz Eylül University Department of Emergency Medicine (EMDEU). The number of incidents was higher in the spring (30.9%) and in October (9.7%).

The mean time that elapsed between exposures and calls was 5.2±5.7 hours. The median time elapsed between exposures and calls was 3.5 (min: 0.05, max:48) hours. Of the poisoning cases, 72.6% were (257) women, with a mean age of 24.1±15.4 years; overall, 41.2% (146) were children (1 month to 18 years) and 58.2% (206) were adults (19 to 90 years). The median age of all cases was 20 (min: 1 month, max: 90) years; for women, this was 20 years (min: 6 months, max: 90) and for men it was 25 (range between 1 month to 80 years old), respectively (Table 1). Toxicity was acute in 95.2% (337) of the cases and ingestion was the most common route of exposure. Intentional exposure was significantly higher in women than in men (88.2% vs. 68.2% for all age groups; $\chi^2=62.08$, $p<0.001$ for children; $\chi^2=42.82$, $p<0.001$ for adults; $\chi^2=98.55$, $p<0.001$ for all age groups) and in adults than in children (64.0% vs. 33.9%; $\chi^2=25.00$ $p<0.001$). Unintentional exposure in children between 0 and 6 years of age was significantly higher than in children between 7 and 18 years of age (85.7% vs. 14.3%; $\chi^2=17.86$, $p<0.001$).

When assessed for poisoning severity at the time of the call, 38.4% of patients (136) were symptomatic (Table 1). Signs and symptoms of the patients admitted to EMDEU are presented in Table 2. Signs and symptoms were found to be significantly more prevalent in adults than in children ($\chi^2=8.22$, $p<0.01$). Serum potassium levels were measured in 31.7% (13) of patients admitted to EMDEU. In our laboratory, the normal range of serum potassium was 3.5-5.1 mmol/L. The level in eight patients (61.5% of serum potassium level measured cases) was regarded as low (mean 3.02 ± 0.1 mmol/L). Also, hyperglycaemia was observed in 17.1% of patients, with the mean blood glucose level being 181.7±12.4 mg/dL.

Concomitant drug and/or substance exposure was positive in 87.8% (36) of patients admitted to EMDEU. Alcohol (2) and drugs acting on the central nervous system (phenprobamate, fluvoksamin, paroksetin etc., 10), bronchodilators (6), vitamins and mineral supplements (6), analgesics (4), antimicrobials (3) and other drugs (7) were the main concomitant drugs/substances. No illicit drug use was reported.

Theophylline concentrations

Serum theophylline concentrations were measured in 18.4% (65) of patients (Table 3). When toxic and non-toxic concentrations were compared, toxic theophylline concentrations were significantly associated with the presence of clinical signs and symptoms ($\chi^2=15.11$, $p<0.001$).

TABLE 1. The demographic and poisoning information of theophylline exposures

	Children ≤18 years		Adults >18 years		Unknown		Total	
	n	%	n	%	n	%	n	%
Gender								
Male	27	31.8	58	68.2	0	0.0	85	100.0
Female	110	42.8	145	56.4	2	0.8	257	100.0
Unknown	9	75.0	3	25.0	0	0.0	12	100.0
Toxicity								
Acute	142	42.1	193	57.3	2	0.6	337	100.0
Chronic	0	0.0	5	100.0	0	0.0	5	100.0
Acute-on-chronic	0	0.0	2	100.0	0	0.0	2	100.0
Unknown	2	20.0	6	60.0	0	0.0	10	100.0
Circumstance								
Intentional	102	35.1	187	64.3	2	0.7	291	100.0
Unintentional	35	76.1	11	23.9	0	0.0	46	100.0
Unknown	9	52.9	8	47.1	0	0.0	17	100.0
Poisoning severity								
Asymptomatic	102	47.7	112	52.3	0	0.0	214	100.0
Mild	37	32.7	74	65.5	2	1.8	113	100.0
Moderate	5	31.3	11	68.8	0	0.0	16	100.0
Severe	1	14.3	6	85.7	0	0.0	7	100.0
Unknown	1	25.0	3	75.0	0	0.0	4	100.0

TABLE 2. Clinical effects of EMDEU cases

	Total	
Clinical effects	n	%
Hypokalaemia	8	19.5
Tachycardia	7	17.1
Hyperglycaemia	7	17.1
Nausea-vomiting	6	14.6
Headache	4	9.8
Dizziness	2	4.9
Shortness of breath	2	4.9
Tremor	1	2.4
Hypertension	1	2.4

EMDEU: Dokuz Eylül University Department of Emergency Medicine

TABLE 3. Distribution of medical outcome of theophylline exposures reported to the Dokuz Eylul University Drug and Poison Information Center by serum theophylline concentration

	Serum theophylline concentration (n=65)			
	Toxic		Non-toxic	
Poisoning severity	n	%	n	%
Asymptomatic	19	39.6	8	47.1
Mild	18	37.5	9	52.9
Moderate	8	16.7	0	0.0
Severe	3	6.3	0	0.0
Total	48	100.0	17	100.0

Treatment and outcome

Treatment outcomes could be assessed for all of the EMDEU patients (Table 4). Of these patients, 39 recovered and were discharged, while two patients died despite treatment. Theophylline was the only agent of poisoning and the poisoning severity score was severe in these two deaths. The 25 year-old woman took theophylline in an acute setting for suicide, while the other patient (90 year-old woman) experienced acute chronic theophylline exposure. The mean length of hospitalisation was 17.1±1.3 (range 2 to 33) hours.

DISCUSSION

This study presents theophylline exposures reported to the Dokuz Eylül University DPIC over a period of 19 years. It is the biggest descriptive study analysing theophylline exposure to date in our country. DPIC calls based on the spontaneous

TABLE 4. Distribution of applied and recommended treatment attempts

	Applied before calling DPIC		Recommended by DPIC	
Treatment methods	n	%	n	%
Observation alone	91	25.7	109	30.8
Mechanical emesis	3	0.9	0	0.0
Gastric lavage alone	24	6.8	2	0.6
Activated charcoal alone	30	8.5	112	31.6
Gastric lavage and activated charcoal	69	19.5	96	27.1
Specific antidote treatment	0	0.0	1	0.3
Haemodialysis/haemoperfusion	0	0.0	1	0.3
Others	137	38.6	33	9.3
Total	354	100.0	354	100.0

DPIC: Dokuz Eylül University Drug and Poison Information Center

reports of poisonings give a general idea about the epidemiology of theophylline exposure in Turkey. In our study, during a 19 year period, 354 theophylline exposures were reported, accounting for 0.4% of all calls to the DPIC. Of these exposures, 41 cases were admitted to the Dokuz Eylül University Department of Emergency Medicine (EMDEU). Epidemiological data on theophylline exposures are limited. The American Association of Poison Control Centers (AAPCC) reported over 330 telephone enquiries regarding children and adults who were thought to have been poisoned with theophylline (1.5% of asthma therapeutics) in 2009. Additionally, the rate of poisonings with theophylline was almost 0.4% of fatal non-pharmaceutical and pharmaceutical exposures according to the same report of the AAPCC (6). Shannon et al. (4) reported 356 theophylline poisonings in a 10-year period. In our study, theophylline accounted for 0.4% of the poisonings reported to DPIC.

Theophylline is the prototype drug of the non-selective phosphodiesterase inhibitors. Despite decreasing use, theophylline is still a drug of choice for the treatment of neonatal apnoea, asthma, and chronic obstructive pulmonary disease. Adverse effects could be observed even in the case of therapeutic doses of theophylline (7). It has been reported that 67.5% of the patients developed toxicity following theophylline administration in inpatient or emergency department settings (8). Toxic effects include nausea, vomiting, abdominal pain, tachycardia, mild transient hypertension, hypotension, significant dysrhythmias, metabolic abnormalities (hypokalaemia, hypercalcaemia, hypophosphataemia, hypomagnesaemia, hyperglycaemia, metabolic acidosis, respiratory alkalosis) and seizures (3, 9, 10). Theophylline is rapidly absorbed, within 30 minutes to 1 hour following oral administration, with early clinical signs and symptoms. Sustained-release preparations have delayed kinetics (10). In our study, clinical signs and symptoms were present in 38% of the theophylline exposure cases reported to DPIC at the time of calls, and mild findings were recognised for one third of them. Severe findings were present in 2% of symptomatic cases. Severe symptoms were found in 27% of theophylline overdoses in the study of Shannon et al. (4). The most common clinical effects found in patients admitted to EMDEU were hypokalaemia, tachycardia, hyperglycaemia, nausea, vomiting, and headache. The most common signs and symptoms of theophylline toxicity were reported as tachycardia, vomiting, tremor and myoclonus (3). Evidence supports the fact that theophylline stimulates the catecholamine-mediated pathway, with the antagonism of insulin by epinephrine. Hyperglycaemia is a frequent finding due to the aforementioned mechanism in theophylline poisoning. Sessler et al. reported that the rate of hyperglycaemia in theophylline toxicities was 62% in their study (3). In other studies, hyperglycaemia rates were found to be 72%, 89% and 93%, respectively (4, 11, 12). Additionally, in the study of Shannon et al., the mean blood glucose level was 180 mg/dL for theophylline poisoning cases. While the rate of hyperglycaemia was 17% for EMDEU cases, the mean blood glucose level was 181 mg/dL, similar to Shannon's report. The serum theophylline level was regarded as toxic in 74% of EMDEU theophylline-measured cases. Clinical signs and symptoms were found to be significantly more prevalent in cases with toxic theophylline levels than in patients with non-toxic levels ($p<0.001$). Theophylline levels should be monitored every 2 to 3 hours to ensure decreasing values (9).

The poisoning incidence has been reported to be highest in the spring and summer in the previous studies (13-15). In parallel with these findings, we found that theophylline poisonings were reported mostly in the spring.

A wide distribution of ages is observed in theophylline poisoning, owing to different treatment indications. It has been reported that the age distribution of the patients with theophylline toxicity is between 3 months and 98 years, with the mean age of 34.5 years (4). In our study, the age distribution of the patients was between 1 month and 90 years, with a mean age of 24.1 years (6). Gender distribution differs between the studies of theophylline toxicity with both male and female dominance (3, 4). Females accounted for 72% of the cases in our study.

Theophylline exposure causes acute, chronic or acute-on-chronic toxicity. Shannon found that 45.5% of poisonings were acute, 40% were chronic, and 14% were acute-on-chronic (4). We found that 95% of the cases presented with acute toxicity, while 1.4% and 0.6% presented with chronic and acute-on-chronic toxicities, respectively.

Drug, herbal medicine and food interactions with theophylline have all been previously determined (16-18). Alcohol

co-administration is believed to be a risk factor for the development of theophylline toxicity (17, 19). Thirty-six patients were found to have taken alcohol or drugs other than theophylline in our study. An increased severity of toxicity might be expected in patients with concomitant drug and/or substance use, especially with alcohol and drugs acting on the central nervous system.

In this study, we observed that intentional theophylline exposures (suicide attempts or abuse) were more common than unintentional exposures, except in children younger than 6 years. We found that young adults between the ages of 19 and 29 years and children between the ages of 13 and 18 years were the most vulnerable to poisonings. Similar findings have been reported in previous case series from Turkey (13, 20-22). Higher rates of intentional theophylline exposure were also found in females in all of the age groups.

In theophylline toxicity, the preferred type of gastric decontamination is gastric lavage followed by activated charcoal for toxic ingestion. Gastric lavage may be useful for several hours after the ingestion of sustained-release preparations. Because of the high risk of seizure, mechanical emesis is not recommended. Since theophylline undergoes significant enterohepatic circulation, multiple-dose-activated charcoal can enhance elimination (9, 23). Haemodialysis should be considered if the plasma theophylline concentration exceeds 40 to 60 μg/mL in chronic overdose and/or significant signs of poisoning (cardiac dysrhythmias, haemodynamic instability, seizures) are present (7, 10). In our study, recommended observation procedures were higher in theophylline exposures admitted to EMDEU than observation procedures applied before DPIC inquiries (26% and 12%, respectively). This high observation rate may be explained by the fact that poisoned patients were transported to EMDEU after performing the gastrointestinal decontamination methods since EMDEU was known as a reference hospital of the Izmir region. While only gastric lavage recommendations were few, the high rate of multiple-dose activated charcoal recommendations was not surprising. This high rate may be explained by the fact that theophylline undergoes significant enterohepatic circulation and multiple-dose-activated charcoal can enhance elimination. Additionally, performed gastrointestinal decontamination procedures were higher than recommended gastrointestinal decontamination procedures by DPIC (83% and 66%, respectively). DPICs have an important role in changing the habit of performing gastrointestinal decontamination for every patient suspected of theophylline poisoning. However, both rates of gastrointestinal decontamination were higher than those recommended by AACT and EAPCCT (24, 25).

In our study, the average length of hospital stay was 17 hours for theophylline exposure. The sustained release preparations of theophylline ingestions can result in delayed and prolonged central nervous system and cardiovascular toxicity and sustained toxic serum theophylline levels. Also, severe theophylline poisoning causes prolonged hospitalisation.

The mortality rate for patients with theophylline toxicity is estimated to be 10% (3). In a study from Iran, theophylline-induced fatalities occurred in 2.4% of all drug poisonings (15). The AAPCC reported that 0.35% of all medicine-induced fatalities resulted from theophylline. Additionally, in the same study, it was emphasised that all fatalities were among 78 to 91 year-old patients (6). In our study, two (4.6%) fatalities were diagnosed as theophylline exposure being the primary cause. Our mortality rate may be lower than the actual mortality rate because DPIC receives intentional but not obligatory mortality reports and there are limitations for telephone follow-ups regarding mortalities. One patient, a 90 year-old woman, died from chronic theophylline ingestion and the other patient, a 25 year-old woman, died from theophylline overdose in an acute setting for suicide. Rogers et al. found that age was associated with the risk of death from theophylline toxicity (26). The toxicity of theophylline is affected by many variables which necessitate carefully managed treatment modalities. Age, smoking, diet, underlying diseases such as congestive heart failure, and drug interactions all contribute to a change in the prognosis of theophylline poisonings. Patients aged 60 years or older and those aged 3 years and younger are at increased risk of developing life threatening theophylline toxicity, as are patients with significant underlying medical conditions. Physicians must be alert to the diagnosis of theophylline toxicity and to its risk factors in order to prevent poor prognosis.

Acute and chronic exposure to theophylline can cause serious signs and symptoms of poisoning. Additionally, with a narrow therapeutic range, toxicity could be observed, even with therapeutic doses of theophylline. Physicians must be alert to the increased risk of theophylline toxicity in children and elderly patients. Serum theophylline monitoring is important for the diagnosis and management of treatment modalities for theophylline poisonings. Multiple-dose-activated charcoal should be considered in patients with serious or potentially life-threatening theophylline overdose. Additionally, poison control centres should play an important role in guiding the management of theophylline poisoning.

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