Amitriptyline Intoxication in Children
Twenty Years' Experience in a Tertiary Care Center in Turkey

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Background: Amitriptyline ingestion is an important cause of poisoning morbidity and mortality in Turkey and other countries. In contrast to adults, data concerning amitriptyline intoxication in children are limited. The purpose of this study was to investigate amitriptyline intoxication findings in the pediatric population, based on age groups and reported dosages.

Methods: The medical records of 192 patients admitted to the Karadeniz Technical University Medical Faculty Farabi Hospital Pediatric Emergency Department, Turkey, due to amitriptyline intoxication in 1997–2017 were examined retrospectively. Patients were divided into 6 groups based on amitriptyline doses and 4 groups based on age. Complete blood count, blood glucose, serum electrolytes, renal and liver function tests, coagulation tests (prothrombin time and partial thromboplastin time), and blood gas analysis were studied in all patients. Electrocardiography was performed on all children, and chest radiography and electroencephalography on those with respiratory or central nervous system symptoms.

Results: Amitriptyline intoxication was most frequently observed between the ages of 1 and 4 years. The most common signs and symptoms observed at time of hospital admission were lethargy and drowsiness (45.3%), sinus tachycardia (19.2%), and nausea and vomiting (13%). The most common laboratory finding was hyperglycemia (17.7). Six patients were intubated because of respiratory failure, and mechanical ventilation was initiated in these cases. One patient with amitriptyline overdose had persistent supraventricular tachycardia. Four children died due to amitriptyline intoxication.

Conclusions: Tricyclic antidepressant intoxication is a leading cause of mortality and morbidity in children. It is therefore particularly important to identify the clinical and laboratory findings that develop with high-dose consumption.

Key Words: amitriptyline, childhood poisoning, intoxication, tricyclic antidepressant

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Childhood poisoning is a significant worldwide health problem and a preventable cause of morbidity and mortality.[1] Epidemiological studies from Turkey have reported that children constitute one-third of patients admitted to the emergency department due to poisoning and that more than half of these are children younger than 6 years with accidental intoxications. One of the most common sources of intoxication, after multiple drug intake and corrosive poisoning, is tricyclic antidepressants (TCAs).[2–5]

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Methods commonly used by adolescents for purposes of suicide include hanging, exhaust fume inhalation, and medication overdoses including acetaminophen, benzodiazepines, and TCAs.[6–8] Intoxications caused by the TCA amitriptyline are very important because of their adverse effects and potentially fatal outcomes. As with other TCAs, many of the adverse effects of amitriptyline are the result of antimuscarinic effects. Amitriptyline may also cause adverse cardiovascular, respiratory, and neurological effects.

We think that the high level of antidepressant use in our region increases the risk of accidental intoxication in children. Although the clinical and laboratory findings related to poisoning due to suicide in adults have been well defined, findings concerning ingestion at low doses are less well known. The aim of this study was therefore to investigate the clinical and laboratory findings of amitriptyline intoxication involving different doses and ages.

METHODS

This retrospective study evaluated cases of amitriptyline intoxication admitted to the Karadeniz Technical University Medical Faculty Farabi Hospital Pediatric Emergency Department, Turkey, between January 1, 1997, and December 31, 2017. Inclusion criteria included single-substance poisoning with amitriptyline among patients younger than 17 years. It was the standard of care at the study institution to inquire about the maximum possible ingested dose. Complete blood count, blood glucose, serum electrolytes, renal and liver function tests, coagulation tests (prothrombin time and partial thromboplastin time), and blood gas analysis were recorded in all cases. Electrocardiography (ECG) was also evaluated for all children. Electroencephalography (EEG) was assessed in children with central nervous system symptoms such as convulsion or change of consciousness. Potential subjects were excluded if full data under study were unavailable, or if they had a history of vomiting immediately after drug ingestion and remained asymptomatic. Data were ascertained by electronic medical record search for *International Classification of Diseases, 10th Revision* codes T43.0 and T43.2.

Three hundred sixteen patient charts were identified for study review. Forty-three patients did not have amitriptyline intoxication and did not meet inclusion criteria because of miscoding. The records of 26 patients could not be retrieved and were not included. Forty-five patients were excluded from the study because their TCA ingestions were not confirmed by urine toxicology testing. Of the remaining 202 patients, 10 were excluded because of missing data on dose. The study was thus completed with 192 patients.

Medical records were abstracted by pediatricians who were blind about this study. Subjects were assessed in terms of sex, age, recorded family history of psychiatric diagnosis, reason for drug intake, time between substance intake and hospital admission, estimated maximum amount of amitriptyline ingested (mg/kg per dose), presenting symptoms, clinical signs, laboratory findings, emergency procedures, complications, length of

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hospitalization, and prognosis. In order to identify which dose of amitriptyline caused which adverse effect, patients were divided into 6 comparison groups based on estimated doses ingested: less than 5, 5 to 9, 10 to 19, 20 to 29, 30 to 39, and greater than 50 mg/kg per dose. The range of 40 to 49 mg/kg per dose was excluded because no patients were included in it. Statistical analysis was performed using Statistical Package for Social Sciences software (SPSS 13.0; SPSS Inc, Chicago, Ill).

RESULTS

Demographic data are shown in Table 1. The median age of patients was 4 years, and the mean age of the patients was 5.92 ± 4.0 years (range, 2–17 years), 54% (n = 103) being boys and 46% (n = 89) girls. Amitriptyline ingestion was most frequently observed between the ages of 0 and 4 years (64%, n = 124), whereas 24% (n = 45) of patients were aged 5 to 11 years, and 12% (n = 23) were 12 to 17 years old. Eighty-six percent (n = 166) of cases involved accidental intake, whereas 14% (n = 26) represented attempted suicide. Seventy-three percent (n = 19) of the suicide attempters were female, and 27% (n = 7) were male, with ages ranging between 11 and 17 years. Three patients attempting suicide were 11 years old, the youngest age at which such attempts were observed.

The mean time elapsing between poisoning and admission to hospital was 3.20 ± 2.98 hours (0.5–15 hours). Ninety-four percent (n = 181) of patients had a family history of psychiatric diagnoses, and the amitriptyline source was a family member. The others were using amitriptyline for psychiatric problems. Seventy-four percent of cases involved amitriptyline ingestion of less than 10 mg/kg per dose. Mean hospitalization time for amitriptyline intoxication was 38.2 ± 20.25 hours (6–96 hours) among surviving patients. No previous intervention had been performed in 11% (n = 21) of all cases.

The number of asymptomatic patients was 76 (39.5%). The majority of these patients had a drug dose of less than 4.9 mg/kg. The most common signs and symptoms observed at time of hospital admission were lethargy and drowsiness, sinus tachycardia, and nausea and vomiting. The most common laboratory finding was hyperglycemia. Clinical and laboratory findings based on doses of amitriptyline ingested are shown in Tables 2 and 3. No drug-related changes such as thrombocytopenia, leukopenia, leukocytosis, bicytopenia, or pancytopenia were observed at complete blood count.

Only 23 patients were evaluated with EEG. Six patients, without active seizures, with drug intake exceeding 30 mg/kg per dose exhibited diffuse slowing at EEG. The EEGs of the other patients were evaluated as normal. Suspicious sharp discharges were observed in the temporal and frontal areas of 1 patient who experienced seizure while in the intensive care unit.

Activated charcoal was administered to some patients presenting within the first 2 hours. Because the benefit of this treatment is controversial, it was not given to patients with low-dose intoxication. Because the benefit of repetition of this treatment was also not known, the treatment was repeated in cases with drug intakes exceeding 50 mg/kg per dose. There are therefore no reliable records of the effect of this treatment on prognosis. Although insufficient data were available concerning the effect of this treatment on prognosis, 4 patients who died had received activated charcoal. Patients with a QRS duration longer than 100 milliseconds were given sodium bicarbonate therapy. The patient with seizure was treated with benzodiazepine.

Six patients were intubated because of respiratory failure, had mechanical ventilation initiated, and were treated with hemoperfusion. One of these patients with amitriptyline overdose demonstrated persistent supraventricular tachycardia (SVT), and another had profound hypotension; both of these were in group of patients believed to have taken more than 50 mg/kg. The other 4 children (2%) died due to amitriptyline intoxication in the intensive care unit; 2 of them were 4 years old, whereas the other 2 were 5 and 6 years old. These had all taken the drug by accident, and all had refractory hypotension. The estimated amounts of amitriptyline ingested by the nonsurviving patients were 96, 95, 86, and 75 mg/kg per dose. Average survival was 3 days (range, 1–5 days). All had QRS durations longer than 100 milliseconds and received sodium bicarbonate therapy and hemoperfusion. No patients had kidney or liver failure or coagulation defects. Prothrombin time, international normalized ratio, and transaminase elevation were low in a small number of patients.

TABLE 1. Demographic Findings of Children Younger Than 17 Years Treated for Amitriptyline Ingestion

	Range of Age (n) (%)		
	1–4 y (124) (64)	5–11 y (45) (24)	6–12 y (23) (12)
Sex, n (%)			
Female	55 (62)	21 (24)	13 (14)
Male	69 (67)	24 (23)	10 (10)
Accidental	124 (75)	42 (25)	—
Suicide	—	3 (12)	23 (88)
Estimated dose, mg/kg per dose, n (%)			
<5	55 (80)	14 (20)	—
5–10	37 (51)	17 (23)	19 (26)
10–20	24 (65)	9 (24)	4 (11)
20–30	3 (75)	1 (25)	—
30–40	1 (33)	2 (67)	—
≥50	4 (66)	2 (37)	—

DISCUSSION

One hundred ninety-two cases of amitriptyline intoxication admitted to the Pediatric Emergency Service between January 1, 1997, and December 31, 2017, were examined retrospectively.

Tricyclic antidepressants commonly used as antidepressants, and especially amitriptyline, may cause various different adverse effects, including tachycardia, mydriasis, dry mouth, warm flushed dry skin, delayed gastric emptying, slowed intestinal peristalsis or even ileus, constipation, urinary retention, agitation, headache, fatigue, anxiety, increased intraocular pressure, blurred vision, drowsiness, weakness, dizziness, restlessness, anorexia, nausea, ophthalmoplegia or paralysis of gaze, acute pancreatitis palpitations, hypertension, tremors, myoclonus, confusion, delirium, and lethargy.[9,10] Life-threatening cardiac arrhythmias and conduction disturbances, acute myocardial infarction, abrupt changes in level of consciousness, coma, convulsions, hypotension, pulmonary complications such as respiratory depression, sudden apnea, aspiration pneumonia, adult-type respiratory distress syndrome, pulmonary edema, and sudden death can also be observed in severe TCA intoxications.[11–13]

The most common clinical findings in our study were lethargy and drowsiness (45.3%), sinus tachycardia (19.2%), and nausea and vomiting (13%). Caksen et al[14] reported tachycardia (47.7%), lethargy (45.4%), convulsion (25%), and coma (20.4%) as the most common clinical findings in their study.

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TABLE 2. Clinical Findings Children With Amitriptyline Poisoning

Ingested Dose (mg/kg), n (%)	<4.9, 69 (36)	5–9.9, 73 (38)	10–19.9, 37 (19.2)	20–29.9, 4 (2.1)	30–39.9, 3 (1.6)	>50, 6 (3.1)	n (%), 192 (100)
Clinical findings							
Lethargy-drowsiness		41	35	3	2	6	87 (45.3)
Sinus tachycardia	3	14	17	2	1		37 (19.2)
Nausea and vomiting	2	14	7	2			25 (13)
Dizziness		13	5	1			19 (9.9)
Convulsion			5	3	2	6	16 (8.3)
Urinary retention			6	3	2	5	16 (8.3)
Ataxia		1	13	1			15 (7.8)
Mydriasis			7	1	1	5	14 (7.2)
Arrhythmia			5	1	2	5	13 (6.7)
Coma				3	3	6	12 (2.3)
Hypotension			1	3	1	5	10 (5.2)
Hypertension			7				7 (3.6)
Dry mouth		1	6				7 (3.6)
Respiratory depression						6	6 (3.1)
Tremor		1	2				3 (1.5)
SVT						1	1 (0.5)

The most common clinical findings determined by Olgun et al[15] were lethargy (76.9%), tachycardia (57.7%), coma (48.1%), and Babinski sign (28.8%). The most common laboratory findings in that study were hyponatremia and leukocytosis.[15] The most common laboratory finding in our study was hyperglycemia.

Cardiovascular toxicity due to amitriptyline intoxication is characterized by ECG abnormalities, arrhythmias, and hypotension.[15,16] The principal mechanism of cardiac toxicity is cardiac sodium-channel blockade, which increases the duration of the cardiac action potential and refractory period and delays atrioventricular conduction. The most common cardiovascular adverse effect is sinus tachycardia. This has been reported in 47.7% to 57.7% of cases of amitriptyline intoxication.[14,15] Güloglu et al[16] described sinus tachycardia as the most common clinical finding in 110 patients older than 15 years. Sinus tachycardia was also the most common cardiac finding in our study, being observed in 18.8% of patients. It was most frequent in patients with ingested amitriptyline doses of 10 to 19.9 mg/kg. Electrocardiography changes include prolongation of the PR, QRS, and QT intervals; nonspecific ST segment and T wave changes; atrioventricular block; right axis deviation; and the Brugada syndrome pattern.[17]

In our study, prolongation of the QRS segment (>100 milliseconds) was observed in 11 patients and SVT in 1. These ECG changes were determined in patients who ingested doses exceeding 10 mg/kg. One patient with amitriptyline overdose with

TABLE 3. Patient Laboratory Findings

Ingested Dose (mg/kg), n (%)	<4.99, 69 (36)	5–9.99, 73 (38)	10–19.99, 37 (19.2)	20–29.99, 4 (2.1)	30–39.99, 3 (1.6)	>50, 6 (3.1)	n (%), 192* (100)
Laboratory findings							
Hyperglycemia (>120 mg/dL)		12	18			4	34 (17.7)
Respiratory acidosis		7	5	1	1	2	16 (8.3)
Metabolic acidosis				1	1	3	5 (2.6)
Respiratory alkalosis			1	1			2 (1)
Hyponatremia (<135 mg/dL)			5	1	2	2	10 (5.2)
Hypernatremia (>150 mg/dL)					1		1 (0.5)
Elevations of INR		2	1				3 (1.5)
Elevations of PT		1	1				2 (1)
Elevations AST and ALT		7	2				9 (4.6)
Prolongation of the QRS				5	4	2	11 (5.7)

INR and PT are important for coagulation. AST and ALT are liver enzymes. ALT, alanine aminotransferase; AST, aspartate transaminase.

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persistent SVT was treated with adenosine. QRS segment prolongation was recorded in all patients who were followed up in the intensive care unit with mechanical ventilation support and in the patient who died due to amitriptyline intoxication.

Hyponatremia is a common laboratory finding in intoxications involving TCAs. Paksu et al[18] reported hyponatremia as the most frequent clinical finding. That study evaluated the clinical findings of 250 patients with amitriptyline intoxication, including 162 pediatric patients.[18] This study is one of the largest series in the literature for the childhood amitriptyline poisonings. In Paksu and colleagues' study, the most common pathological clinical findings were alteration of consciousness, sinus tachycardia, and loss of deep tendon reflexes at time of admission. The most frequently observed laboratory abnormalities on admission to hospital were hyponatremia, hyperglycemia, and leukocytosis. The most common clinical findings in our study were lethargy, drowsiness, and sinus tachycardia. The data available in our study were not sufficient to evaluate deep tendon reflexes or the Babinski reflex. We observed hyponatremia in 10 patients, all of whom had ingested doses higher than 10 mg/kg. In addition to hyperglycemia, 3 patients in Paksu and colleagues' study had hypoglycemia, although this was not observed in any cases in our study.

Twenty-three patients were evaluated by EEG. Only 6 exhibited diffuse slowing, and 1 had suspicious epileptic activity. We think that EEGs were normal because patients were not evaluated using EEG in the first hours under emergency conditions. Electroencephalography was capable of being performed when consciousness was normal, and these therefore resulted normal. Electroencephalography was normal in all patients with convulsion, except for one. Patients with diffuse slowing at EEG had ingested doses exceeding 30 mg/kg per dose.

Amitriptyline intoxication continues to be a leading cause of mortality and morbidity in childhood.[19–21] Caksen et al[14] reported a mortality rate of 4.5% in amitriptyline intoxication. The lowest dose ingested among nonsurviving patients in that study was 36 mg/kg per dose. Our mortality rate in amitriptyline intoxication was 2%. All these patients were younger than 5 years, and quantities of amitriptyline ingested in fatal cases were believed to exceed 75 mg/kg per dose.

The Extracorporeal Treatments in Poisoning workgroup reported about the use of extracorporeal treatments in poisoning after the end of extensive literature search. The workgroup concluded that TCAs are not dialyzable.[22] Although there are patients who are thought to benefit from these treatments, it is difficult to directly correlate their recovery with hemodialysis. At our hospital, 6 critically ill TCA-poisoned children were treated with hemoperfusion added to routine critical care support, and 2 improved and 4 died.

Because amitriptyline is frequently used for purposes of suicide in adults, the data for this field are better known. Because the number of drug intakes for purposes of suicide was very low in the present study, no comparison was possible with accidental drug intake. All severe complications and deaths resulted from accidental ingestion, which highlights the dangerous nature of these medications and which calls for heightened safety efforts.

The most important limitation of our study is that blood amitriptyline levels could not be determined. Another limiting factor was that electrocardiograms were not available for standardized review in all patients, even though prolongation of the QRS, PR, and ST segment was present in the records. Moreover, we were unable to evaluate mild leukocytosis present at time of examination when we examined the records retrospectively because the presence of infection had not been excluded in these patients.

We think that clinical and laboratory findings may not have emerged completely because most of the drug ingestions were accidental and because of the dose ranges involved. However, we think it is important to emphasize the clinical manifestations of low-dose amitriptyline intoxication.

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