

## Acute Amitriptyline Poisoning in Childhood: Experience of a Single Center

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### Abstract

**Objective:** High-dose amitriptyline is a common cause of childhood poisoning. The aim of this study was to evaluate the demographic and clinical characteristics of 126 children who presented with amitriptyline poisoning.

**Material and Methods:** The medical records of children who were admitted to the Pediatric Intensive Care Unit for amitriptyline poisoning between January 1986 and March 2011 were retrospectively evaluated.

**Results:** High-dose amitriptyline is a common cause of childhood poisoning. An increase in the number of cases of amitriptyline poisoning was observed in recent years, with 62.7% of all cases being accidental whereas 37.3% of cases were attempted suicides. The mean age of accidental cases of poisoning was 2.9±1.4 years compared to 14.2±1.9 years for suicidal cases (p<0.01). Patients who accidentally ingested amitriptyline presented to a health care facility in a shorter period than those who took the drug with suicidal intent (respectively 2.4±2 hours vs. 4.2±4.3 hours; p<0.01). In 78.3% of cases, the drug was stored in place easily accessible to children. While 37.3% of patients took the drug at toxic doses, in 47.6% of patients the amount of amitriptyline ingested was below the toxic dose. Seventy-one percent of patients had neurological symptoms on presentation. Gastric lavage was the most commonly utilized treatment modality (78% all of cases). Only one patient who had accidentally consumed the drug at a dose of 15mg/kg died.

**Conclusion:** There is a dire need for reforms in political, industrial and public health policies regarding the packaging and storage of medications which are a common cause of accidental drug poisoning with potentially severe consequences.

**Key Words:** Amitriptyline; Poisoning; Children; Plasma Exchange.

### Çocukluk Çağında Akut Amitriptilin Zehirlenmesi: Tek Merkezin Deneyimi

#### Özet

**Amaç:** Yüksek doz amitriptilin çocuklarda ciddi ilaç zehirlenmesinin en yaygın nedenlerinden biridir. Bu makalede, amitriptilin zehirlenmesi olan 126 çocuğun demografik özellikleri ve klinik bulguları gözden geçirilmiştir.

**Gereç ve Yöntem:** Ocak 1986 ve Mart 2011 tarihleri arasında amitriptilin zehirlenmesi nedeniyle Çocuk Yoğun Bakım Ünitesine yatırılan 0-16 yaş arası çocukların tıbbi kayıtları retrospektif olarak değerlendirildi.

**Bulgular:** Son yıllarda amitriptilin zehirlenmelerinin artmış olduğu görüldü. Zehirlenmelerin %62.7'si kaza nedenli, %37.3'ü ise intihar amaçlı idi. Kaza nedenli zehirlenmelerin yaş ortalaması 2.9±1.4 yaş, intihar amaçlı zehirlenmelerin yaş ortalaması 14.2±1.9 yaştı (p<0.01). Kaza nedenli zehirlenmelerden daha erken sağlık kuruluşuna başvurmuşlardı (sırasıyla 2.4±2 saat, 4.2±4.3 saat, p<0.01). Kaza nedenli zehirlenmelerin %78.3'ünde ilacın, çocuğun kolaylıkla ulaşabileceği yerde olduğu görüldü. Hastaların %37.3'ünün aldığı ilaç dozu toksik dozun üstünde %47.6'sının aldığı ilaç dozu toksik dozun altında idi. Başvuru anında hastaların %71'inde santral sinir sistemine ait zehirlenme bulgular gözlendi. Mide yıkama en yaygın kullanılan tedavi yöntemi idi (%78). Kaza nedenli 15 mg/kg ilaç alan bir hasta kaybedildi.

**Sonuç:** Sık görülen ve ciddi toksisiteye neden olan ilaçlarla zehirlenmelerin önlenmesi amacıyla ambalajlama ve ulaşılabilirlik koşullarının endüstriyel, toplumsal ve politik açıdan gözden geçirilmesi önerilir. Ayrıca yüksek doz amitriptilin alımlarında en kısa sürede plazma değişimi uygulanması seçilmiş hastalarda tercih edilebilecek tedavi alternatifidir.

**Anahtar Kelimeler:** Amitriptilin; Zehirlenme; Çocuk; Plazma Değişimi.

## INTRODUCTION

Amitriptyline is widely used for the treatment of depression, as well as for other disorders such as chronic pain syndrome, nocturnal enuresis, attention deficit and hyperactivity disorder, migraines, neuropathic pain, school refusal and sleep disorders

(1,2). It is an effective and cheap drug which can be purchased without a prescription in Turkey, hence its widespread use.

Amitriptyline poisoning is an important cause of childhood poisoning worldwide, accounting for the majority of cases presenting to emergency departments. It is associated with significant

morbidity and mortality (3). The number of cases of amitriptyline poisoning is on the rise, and while most cases in adolescents occur as a result of suicide, in younger children accidental use is prevalent (3-5).

The aim of this study was to evaluate the epidemiologic and clinical characteristics of patients admitted to the Pediatric intensive care unit (PICU) at our hospital for amitriptyline poisoning. Our goal was to highlight the significance of this rapidly increasing health problem, while also drawing attention to possible solutions for solving it.

## MATERIAL AND METHODS

This retrospective study was undertaken in Ihsan Dogramacı Children's Hospital of the Faculty of Medicine at Hacettepe University. The medical records of children between the age of 0-16 years who were admitted to the PICU for amitriptyline poisoning between January 1986 and March 2011 were systematically reviewed. Information regarding

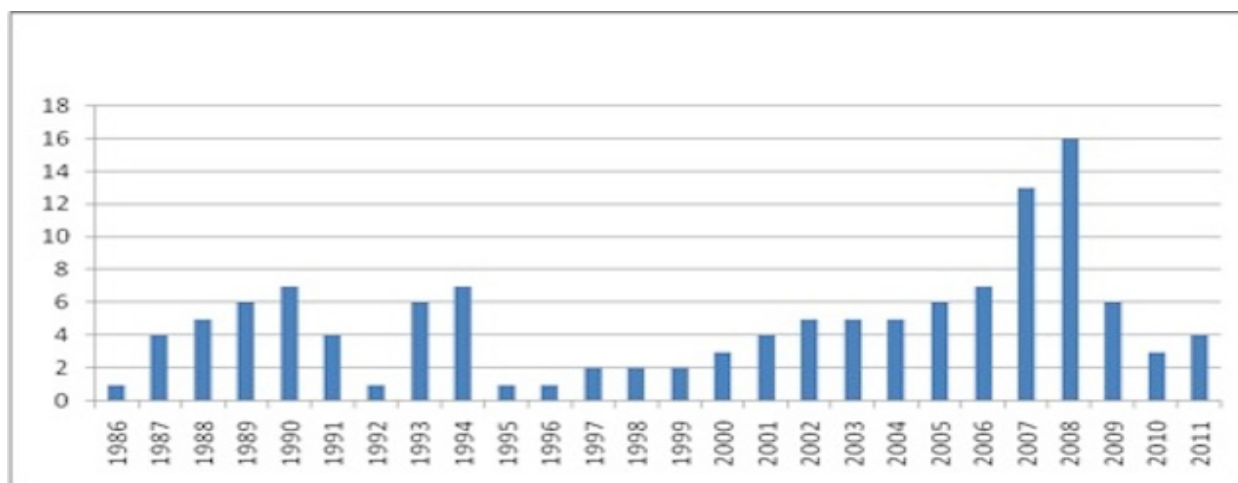
demographic characteristics, amount of drug used, the reason for use, the time between poisoning and presentation to a health facility, presenting signs and symptoms, clinical findings, treatments and survival rates was recorded on pre-prepared forms.

Data was analyzed using SPSS 15.0. The choice of statistical test was made based on the distribution pattern of the variables in question. A p-value of less than 0.05 was considered indicative of statistical significance.

## RESULTS

Evaluation of records spanning 25 years revealed that a total of 126 cases (67 female and 59 male) were admitted to the PICU for amitriptyline poisoning. A breakdown based on year of presentation revealed a gradual increase in the number of cases in recent years, with an observed peak in 2007 and 2008 (Figure 1).

Figure 1. Distribution of amitriptyline poisoning cases according to year of presentation



While 62.7% of the cases were accidental, 37.3% were suicide attempts. The mean age for accidental poisoning with amitriptyline was  $2.9 \pm 1.4$  years compared to a mean age of  $14.2 \pm 1.9$  years for patients with suicidal poisoning ( $p < 0.01$ ). Furthermore, cases of accidental poisoning presented to a health facility sooner than those with suicidal poisoning ( $2.4 \pm 2$  hours vs.  $4.2 \pm 4.3$  hours;  $p < 0.01$ ).

In 37.3% of cases, the dose of amitriptyline taken exceeded the toxic limit of  $>10$  mg/kg, whereas in 47.6% of patients the amount of drug consumed was  $<10$  mg/kg. In 15.1% of patients, the amount of drug taken could not be determined. Patients younger than 6 years of age made up 61% of cases, in all of which poisoning was accidental. In 78.3% of cases,

the drug had been stored in a place easily accessible by children.

Central nervous system findings (loss of consciousness, convulsions, drowsiness, etc.) were present in 71% of patients on presentation (Table 1).

With regard to treatment, gastric lavage was performed in 78% of patients whereas activated charcoal was administered in 74.6% of cases. Other treatments included alkalization in 46%, diuresis in 31% and plasma exchange in 6.3% of patients. All patients received some form of supportive treatment. The only mortality was a 7-year-old male patient with accidental poisoning at a toxic dose of 15mg/kg (mortality rate 0.7%).

**Table 1.** Presenting signs and symptoms of study population

Presenting finding	n	%
Loss of consciousness	46	36.5
Drowsiness	31	24.6
Convulsions	13	10.3
Arrhythmia	6	4.7
Breathing difficulties	3	2.3
Lethargy	3	2.3
Palpitations	2	1.5
Hallucination	1	0.8
Agitation	1	0.8
Speech disorder	1	0.8
Dizziness	1	0.8
Asymptomatic	19	15

## DISCUSSION

Poisoning with antidepressants is a common occurrence. According to data from the national poisoning database in the United States of America, in 2009 antidepressant poisoning accounted for 4.26% of all cases (6). Reported rates of antidepressant poisoning in Turkey range from 9.56% to 34% of all poisoning cases (7).

Amitriptyline is responsible for a large proportion poisoning cases due to antidepressants (4,5,8). Several factors may be responsible for the common occurrence of amitriptyline poisoning: a) it is frequently prescribed due to its low cost and high efficacy, and can even be purchased from pharmacies without a prescription which increases the likelihood of the drug finding its way into households; b) in Turkey, the drug is sold in packages/containers which are easy to open (without child-resistant caps); c) availability of the drug in the form of sugar-coated tablets. The incidence of amitriptyline poisoning is on the rise in our country (4,5). Several studies from Turkey have demonstrated a similar trend in recent years regarding the frequency of poisoning due to amitriptyline (Figure 1).

Childhood poisoning is of greater significance in two particular age groups; below 6 years of age and in adolescents. While poisoning in children younger than 2 years of age is mostly accidental, suicidal poisoning is the most frequent cause in adolescents (9). The poisoning profile of our study population shows a similar pattern of distribution. We also observed that children with accidental poisoning were brought to medical attention earlier than those with suicidal poisoning. This could be because suicidal cases tend to conceal their condition from their families.

The therapeutic dose range for amitriptyline in children is 1-5 mg/kg. Although doses higher than 10 mg/kg are believed to be potentially lethal, severe drug toxicity may also be seen at doses lower than 10

mg/kg (10-12). In our study population, 37.3% of patients had ingested amitriptyline at a dose >10 mg/kg, while a dose of <10 mg/kg was taken by 47.6% of cases. In 15.1% of patients, the dose consumed could not be determined. Although less than half of our patients had taken amitriptyline at a dose less than 10 mg/kg, 85% of them had signs and symptoms of poisoning on presentation, mainly neurological. In very young children, severe toxicity or even death may ensue after consumption of only I-II tablets of amitriptyline or other potentially poisonous drugs (13,14), and in such situations parents and health personnel alike should exercise great care.

In our study, children under the age of 6 comprised 61% of poisoning cases, all of which were accidents which could have been averted had simple measurements been taken. For example, in 78.3% of cases, the drug was stored in an easily accessible location. Our findings are a reminder that a change in legislation regarding the packaging and storage of toxic substances may be required, and that education towards representatives of the pharmaceutical industry as well as the general public may help raise awareness. The poisonous effects of high doses of amitriptyline develop as a result of disrupted reuptake of epinephrine and serotonin in adrenergic and serotonergic neurons due to inhibition of membrane pumps. Common signs and symptoms include tachycardia, arrhythmia, hypotension, respiratory depression, hallucination, varying alterations in state of consciousness and convulsions (4,10). Neurological findings were present in 71% of our patients on admission (Table 1). Similar results were reported in two previous studies by Genc et al (60%) and Oner et al. (56.6%) (4,5).

Convulsions were observed in 13 patients for whom initial intervention was made with intravenous diazepam. For the management of recurrent seizures, phenytoin and phenobarbital were used. With regard to arrhythmias that developed in our study population, complete atrioventricular block was observed in one patient whereas in 5 patients 1. and 2. degree cardiac blocks were detected. For all six cases, alkalization treatment with intravenous NaHCO<sub>3</sub> was performed. A temporary pacemaker was installed for the patient with complete heart block, while only two of the five patients with 1. and 2. degree block required treatment with intravenous lidocaine.

The core treatment of amitriptyline poisoning consists of gastric lavage, activated charcoal, intravenous fluids and bicarbonate, antiarrhythmics and anticonvulsants. A specific antidote has yet to be developed (8,11,15). All the patients in our study received varying combinations of supportive

treatment (gastric lavage in 78%, activated charcoal in 74.6% and alkalization in 46%).

Amitriptyline has a half-life of 21 hours (13-36 hours). The lipophilic nature of amitriptyline facilitates its rapid distribution from the blood circulation into tissues, which accounts for the drug's large volume of distribution (10-20 L/kg). Furthermore, it has a high protein binding capacity (75-90%) (11). These characteristics are responsible of the inefficacy of hemodialysis for the management of amitriptyline poisoning. On the other hand, the efficacy of plasmapheresis in the management of amitriptyline

poisoning has been demonstrated in several case series originating from Turkey, with reported clearance rates of up to 63% (11,15,16). It is widely believed that plasma exchange could be life-saving in patients with high-dose amitriptyline poisoning despite the drug's high protein binding capacity, by resulting in clearance of free and protein bound drug molecules (7,17). All eight patients (6.3%) with high-dose intoxication who presented within 4 hours of drug-ingestion underwent plasma exchange therapy and were subsequently discharged after making full recoveries (Table 2).

**Table 2.** Demographic characteristics of patients who underwent plasma exchange therapy

Case	Gender	Age (years)	Time to presentation (hours)	Dose ingested (mg/kg)	Reason for use of drug	Presenting findings	Outcome
1	Female	1.5	1.5	10	Accidental	Loss of consciousness	Discharge
2	Female	2	1.5	20.7	Accidental	Loss of consciousness, convulsions	Discharge
3	Female	2	1.5	63.3	Accidental	Loss of consciousness, breathing difficulties	Discharge
4	Female	2.5	1	33.3	Accidental	Convulsions	Discharge
5	Female	3	1	15	Accidental	Loss of consciousness, convulsions	Discharge
6	Male	7	0.5	15	Accidental	Loss of consciousness	Discharge
7	Female	12	3	28	Suicidal	Loss of consciousness	Discharge
8	Female	13	4.5	18	Suicidal	Loss of consciousness	Discharge

Deaths due to amitriptyline poisoning are usually a result of myocardial depression, intractable hypotension, ventricular tachycardia or ventricular fibrillation (10). In our study, a 7 year old boy who accidentally ingested more than 15mg/kg of amitriptyline died due to circulatory failure, accounting for a mortality rate of 0.7%.

Amitriptyline poisoning is associated with severe toxicity, the incidence of which has been steadily rising in Turkey in recent years. Most cases, particularly accidental ones, could be prevented by the development of political, industrial and public health policies regarding the packaging and storage of medications. Early plasma exchange therapy is a treatment option that should be reserved for patients with high-dose amitriptyline poisoning presenting with signs and symptoms of severe toxicity.

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