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Lipid Emulsion Treatment in Tricyclic Antidepressant Poisoning in Children: An Observational Cohort Study

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Abstract

Tricyclic antidepressant (TCA) poisonings are among the most common childhood poisonings because of being cheap and readily available. In this manuscript, we aimed to share our experience with Intravenous lipid emulsions (ILE) treatment in addition to basic treatment steps and discussion of effectiveness of treatment in cases of poisoning caused by high-dose TCA intake. From the patients under 18 years of age who admitted to Pediatric Emergency Department due to drug intoxication between January 2014 and December 2019; those who had history of exposure to TCAs were included in our study. In conclusion of examination of six-year patient records, it was determined that there were a total of 619 intoxication cases and 108 (17.4%) of these were TCA poisoning. 21 (19.4%) patients who had hypotension, tachycardia and ECG changes which were refractory to all basic treatment steps were administered ILE. After ILE treatment, a marked improvement was observed in patients' clinical and ECG findings, as well as vital signs. Early administration of ILE treatment in emergency departments for cases with hypotension, conduction disorder, dysrhythmia or widened QRS which are refractory to sodium bicarbonate is thought to prevent potential cardiovascular complications.

Keywords: Intravenous lipid emulsions, tricyclic antidepressant, poisoning, child

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Introduction

Tricyclic antidepressant (TCA) poisonings are among the most common childhood poisonings because of being cheap and readily available. Toxicity profiles of TCAs are almost similar and clinical development of toxicological findings may occur very rapidly and unexpectedly. Following exposure to toxic doses, patients may admit to emergency department with no symptoms, as well as with life-threatening cardiovascular or central nervous system symptoms.[1]

Highlights

- TCA poisonings cause high mortality and morbidity.
- Cardiotoxicity is the most important cause of mortality in TCA poisoning.
- Lack of a known antidote cause challenges in management.
- ILE is the leading one of promising treatment methods for TCA poisoning.

Therapeutic index of TCAs is very low and thus a single sugar-coated tablet may cause a severe poisoning in infancy. Due to their anticholinergic effects gastric emptying delays, intestinal motility slows down so that they are easily absorbed by the intestines and undergo enterohepatic recirculation. This may lead to delayed absorption of the drug and, hence, longer duration of signs and symptoms. Because TCAs have high solubility in lipids, they have wide distribution width in the body and their half-lives are long.[2]

Intravenous lipid emulsions (ILE) have been recently used for poisonings with fat-soluble drugs, although they have been used for parenteral nutrition for years.[3] ILE was used for the first time by Rosenblatt et al.[4] to treat asystole caused by bupivacaine, a local anesthetic.

In this manuscript, we aimed to share our experience of ILE treatment in addition to basic treatment steps in cases of high-dose TCA poisoning and discuss the effectiveness of this treatment.

Material and Method

From the patients under 18 years of age who admitted to pediatric emergency department due to drug intoxication between January 2014 and December 2019; those who had history of exposure to TCAs were included in our study. Following obtaining an Ethics Committee Approval, patients' information, files and data in the hospital's automation system were examined and recorded retrospectively (Ethics Committee Approval number: 2020/2580). Those with missing data were excluded from the study. Information regarding patients' age, gender, age group, time to admission to emergency department, clinical and electrocardiographic (ECG) findings and treatments given, as well as whether the case was an intoxication or suicide were recorded.

According to our pediatric emergency department's treatment protocol for TCA poisonings, once a secure airway is assured, all patients are monitored. Gastric lavage is performed only for those who admitted within an hour after drug intake, while all patients undergo repeat-dose application of activated charcoal. If hypotension occurs during the follow-up, the intervention is fluid loading with normal saline. Patients with seizure are managed with an antiepileptic drug other than phenytoin, as it may enhance the cardiotoxic effect. If a conduction disorder, dysrhythmia or widened QRS develops, a bolus of sodium bicarbonate at a dose of 1-2 mEq/kg is administered and, if needed, it is repeated to achieve pH<7.55 in blood gas analysis. Patients with hypotension, tachycardia and ECG changes which are refractory to these basic treatment steps undergo ILE treatment. %20 ILE lipid solution is administered at a bolus dose of 1-1.5 mL/kg given over 5-10 minutes, followed by 0.25-0.5 mL/kg/min infusion until hemodynamic improvement is achieved for 30-60 minute infusion, with a total maximum dose not exceeding 10 mL/kg/hour.

Statistical Analysis

Statistical analysis of the study was performed by using the Statistical Package for the Social Sciences for Windows ver. 20.0 package program. While the expression n (%) is used for categorical variables, for continuous variables mean ± SD (standard deviation) was used in case of suitability for normal distribution and median (lower-upper limit) values in case of unsuitability for normal distribution. Kolmogorov Smirnov test was used for normality analysis. For analyses of data's distribution and frequency, descriptive analyses were used and for frequency data, Pearson Chi-Square tests were used for comparison of two independent groups. For comparison of means of two independent groups, the independent t-test was used. For all statistical analyses, the level of significance was considered <0.05.

Results

Examination of six-year patient records revealed that there were a total of 619 intoxication cases and 108 (17.4%) of these were TCA poisoning. While mean age of all patients was 7.46±2.67, mean age was 9.38±4.22 for girls and 5.32±2.36 for boys. Of these patients; 57 (52.8%) were determined to be girl and 51 (47.2%) boy. When their causes of admission to emergency department were reviewed, it was observed that 66 (61.1%) admitted with intoxication, 11 (10.2%) with suspected intoxication and 31 (28.7%) with suicide. When the time to admission to emergency department was reviewed, it was determined that 41 (38%) patients had admitted within an hour after drug intake and 67 (62%) more than an hour. Of the drugs they exposured 97 (89.8%) of the patients had taken drug of another adult and 11 (10.2%) their own drug. When the treatment approaches were reviewed, it was determined that all (n=41, 38%) patients who admitted within an hour after drug intake underwent gastric lavage and all (n=108, 100%) treated with activated charcoal. During their clinical follow-ups, it was determined that 25 (23.1%) of the patients developed hypotension, 32 (29.6%) conduction disorder, dysrhythmia or widened QRS and 2 (1.8%) seizures. Distribution of treatments given by gender and age are represented in **Tables 1** and **2**.

Table 1
Distributions of Treatments Given By Gender

	Girls 57 (52.8%)	Boys 51(47.2%)	Total 108 (100%)	p
Gastric lavage	19 (33.3%)	22 (43.1%)	41 (38%)	>0.32
Activated charcoal	57 (52.8%)	57 (52.8%)	108 (100%)	N/A
Loading with normal saline	21 (36.8%)	4 (7.8%)	25 (23.1%)	<0.001
Sodium bicarbonate	24 (42.1%)	8 (15.7%)	32 (29.6%)	0.003
ILE treatment	19 (33.3%)	2 (3.9%)	21 (19.9%)	<0.001

ILE: Intravenous lipid emulsion
N/A: No statistics are computed because activated charcoal is a constant.

Table 2
Distribution of Treatments Given By Age Groups

	<5 yr of age 63 (58.3%)	5-10 yr of age 8 (7.4%)	10-15 yr of age 13 (12%)	>15 yr of age 24 (22.2%)	p
Gastric lavage	33 (52.4%)	2 (25%)	1 (7.7%)	5 (20.8%)	0.003
Activated charcoal	63 (58.3%)	8 (7.4%)	13 (12%)	24 (22.2%)	N/A
Loading with normal saline	6 (9.5%)	2 (25%)	4 (30.8%)	13 (54.2%)	<0.001
Sodium bicarbonate	11 (17.5%)	5 (62.5%)	6 (46.2%)	10 (41.7%)	0.007
ILE treatment	7 (11.1%)	2 (25%)	4 (30.8%)	8 (33.3%)	0.07

ILE: Intravenous lipid emulsion
N/A: No statistics are computed because activated charcoal is a constant.

When the association of gender was examined, 24 (77.4%) of 31 suicide cases were girls which was statistically significant (p=0.004). When their clinical courses were examined, 21 (84%) of 25 patients who developed hypotension were statistically significantly determined to be girls (p<0.001). Examination of ECG findings revealed that 24 of 32 patients who were found to have conduction disorder, dysrhythmia or widened QRS on ECG were statistically significantly determined to be girls (p=0.003).

21 (19.4%) patients who had hypotension, tachycardia and ECG changes which were refractory to all basic treatment steps were administered ILE. After ILE treatment, a marked improvement was observed in patients' clinical and ECG findings, as well as vital signs. Only one (0.9%) patient required monitoring in intensive care unit, who was then discharged with cure. None of the patients developed a complication related to ILE treatment.

Discussion

Marked improvement in clinical and ECG findings and vital signs was observed after ILE treatment in 21 (19.4%) patients who admitted to our emergency department with TCA poisoning and were refractory to all basic treatment steps.

One of the common causes of admissions to pediatric emergency departments is drug intoxications. According to American Association of Poison Control Centers National Poison Data System 2018 data, poisonings with antidepressants rank fifth, with an incidence of 5.22%.[5] In our country, based on the data of Poison Helpline datas, most common agents of poisoning are drugs containing paracetamol (acetaminophen), followed by combined upper respiratory airway drugs and amitriptyline.[6] Again, in a study from our country on forensic case admissions to pediatric emergency departments, patients who admitted with drug intoxication were poisoned most commonly with non-steroid anti-inflammatory drugs with a rate of 25%, followed by antipsychotic and antidepressant drugs with a rate of 19.3%.[7]

In case of exposure to TCA drugs at high doses, toxicity may develop within a duration as short as approximately 30 minutes.[8] Cardiotoxicity is the most important cause of mortality in TCA poisoning. Hypotension and cardiovascular collapse largely result from ventricular arrhythmias and reduced myocardial contractility secondary to sodium channel blockage. Sodium channel blockage prolongs potential of cardiac effect and the refractory period, as well as delays atrioventricular node conduction. This prolongs QRS, QTc and PR intervals, respectively. Toxicity-related acidosis promotes myocardial irritation and dysarhythmogenesis.[9,10] Due to lack of an antidote in poisonings with TCA, gastric lavage and activated carbon are used to minimize drug toxicity, and sodium bicarbonate is used to reduce cardiogenic toxicity.[1] As in our study, there are cases refractory to treatment despite of all these basic treatment methods. This, therefore, has led to search of new treatment methods like ILE treatment.

ILE has arisen as a promising treatment for severe toxicity of lipophilic drugs. Although there are reports for its use in poisonings caused by local anesthetics, anti-arrhythmic drugs, calcium channel blockers, β-blockers, neuroleptics, tricyclic antidepressants, serotonin reuptake inhibitors and phenothiazines,[11-13] there is no sufficient data for its use and dose in pediatric age group. Although by which mechanism ILE acts has not been exactly known, there are some assumptions suggesting that it is multifactorial. The "Lipid-sink" theory postulates that insertion of an expanded lipid phase within intravascular space drains the lipophilic agents from the watery plasma phase, reducing the bioavailability.[14,15] An alternative theory demonstrates that the lipid emulsion enhance presence of myocardial free fatty acids and

reverses the switching from lipid to glucose metabolism in myocardium. Additionally, it is thought that lipid emulsion may oppose to prevention of oxidative phosphorylation in toxic myocardium.[16]

There are some limitations to the current study, which presented the observational data from a single-center with a limited sample size. Therefore, the limited sample size might have prevented drawing definitive conclusions in some analyses. Despite these limitations, this study is significant as one of the first reports of ILE treatment in the pediatric population. Data from more extensive multicenter studies are required to improve the diagnosis, follow-up, and treatment approaches.

Conclusion

TCA poisonings cause high mortality and morbidity because of the fact that they cause toxicity on central nervous system and cardiovascular system. Lack of a known antidote and the fact that there is only a supportive treatment cause challenges in management. ILE is the leading one of promising treatment methods for this issue. Early administration of ILE treatment in emergency departments for cases with hypotension, conduction disorder, dysrhythmia or widened QRS which are refractory to sodium bicarbonate is thought to prevent potential cardiovascular complications. In the literature, there is limited data on ILE treatment in pediatric age group. Larger prospective studies on this issue are required.

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