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In which cases of beta-blocker intoxication in childhood, does hypoglycemia develop more easily?

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ABSTRACT

Objectives: In this study, we aimed to investigate factors which could facilitate the identification of hypoglycemia in beta-blocker (BB) intoxication cases.

Patients and methods: Between November 2020 and November 2021, a total of 136 patients (53 males, 83 females; mean age: 11.6+5.7 years; range, 2 to 17 years) who were admitted to the emergency department with BB poisoning were included in the study. The data on the cases were taken from the hospital's automation system.

Results: The mean systolic blood pressure (SBP) was 86.2±12 mmHg, the mean heart rate (HR) was 72.9±12.2 bpm, and the mean blood glucose level (BGL) was 104.4±42.8 mg/dL. When the relationship between the HR, SBP, and BGL of the cases was examined, there was a poor positive correlation between BGL and HR (r=0.32, p<0.01). No linear correlation was detected between BGL and SBP or between BGL and toxic dose percentage (r=0.23, p=0.06 and r=0.16, p=0.05). A very strong negative correlation was found between the percentage of toxic dose and SBP, and between the toxic dose percentage and HR (r=-0.90, p<0.01 and r=-0.76, p=0.04). There was a weak positive correlation between HR and SBP (r=0.42, p=0.09).

Conclusion: We found a correlation between the decrease in HR and the decrease in BGL. Younger age, female sex, and high dose of the drug facilitated the development of hypoglycemia.

Keywords: Beta-blocker poisoning, hypoglycemia, pediatric emergency.

Poisoning is one of the most preventable causes of child fatalities, and in the United States (US), approximately 1.5 million children are admitted to emergency departments each year due to poisoning.[1] Drugs and corrosive substances are the two largest causes of poisoning worldwide, drugs that affect the central nervous system and cardiovascular system (CVS) constitute the largest number of poisoning cases, and poisoning with beta-blockers (BBs) is particularly common.[1-3] According to the 2004 Toxic Exposure Surveillance System Report, in the US, there were 4,077 BB intoxication case admissions among children under the age of six years old.[4]

In BB poisoning cases, cardiovascular effects (bradycardia, hypotension, myocardial depression, and cardiogenic shock), mental status change, seizure, hypoglycemia, and bronchospasm may occur.[5-7] Beta-blocker poisoning have become more common due to overuse of BBs. These medications are used to treat many diseases, including hypertension, ischemic heart disease, thyrotoxicosis, tremors, portal hypertension, migraine headaches, aortic dissection, arrhythmia, and heart failure. Therefore, this situation makes them easily accessible for children.[8] Cardiovascular effects determine the prognosis.[8-12] The development of hypoglycemia is another clinical condition that is commonly associated with BB intoxication. The development of hypoglycemia is frequently mentioned in the literature; however, this information is mostly based on old case reports and is not very common in daily practice. The mechanisms associated with the development of hypoglycemia depend on inhibiting

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glycogenolysis and gluconeogenesis, which reduces glucose production.[13] Therefore, blood glucose level (BGL) monitoring is vital in BB poisoning cases.

Hypoglycemia is typically defined as a BGL below 60 mg/dL in the presence of symptoms (e.g., sweating, tremor, tachycardia, hunger, lethargy, confusion, irritability, and seizure) or a BGL below 50 mg/dL in the absence of symptoms.[14]

In the literature, there is no study indicating which BB poisoning cases develop into hypoglycemia more frequently. The primary objective of this study was to investigate which characteristics in patients with BB intoxication might be predictive factors for the development of hypoglycemia. The secondary objective was to determine how cardiovascular findings (e.g., heart rate [HR] and systolic blood pressure [SBP]), the main determinants of mortality, were affected in BB poisoning cases.

PATIENTS AND METHODS

This single-center, retrospective, cross-sectional, observational study was conducted at Pediatric Emergency Clinic of Izmir Tepecik Training and Research Hospital Pediatric Poisoning Center between November 2020 and November 2021. Patients aged between 0 and 18 years who were admitted to the emergency department with BB poisoning were included in the study. Patients with a disease affecting the CVS or altering glucose metabolism and those who used drugs that affect these systems were excluded from the study. Finally, a total of 136 patients (53 males, 83 females; mean age: 11.6+5.7 years; range, 2 to 17 years) were included. A written informed consent was obtained from all parents and/or legal guardians of the patients. The study protocol was approved by the Izmir Katip Çelebi University Non-Interventional Clinical Studies Instutional Review Board Ethics Committee (date/no: 2020-GOKAE-0062). The study was conducted in accordance with the principles of the Declaration of Helsinki. The data were obtained from the hospital's automation system. After examining the characteristics of each case, such as age, sex, and the type of drug that they ingested, the HR, SBP, and BGL measurements of the cases were noted. While the independent variable of this study was BGL, its dependent variables were age, sex, HR, and SBP. Cases were categorized as normocardic and bradycardic, considering normal values of HR according to age.[15,16] Cases were also categorized as normotensive or hypotensive, considering the normal values of SBP according to age.[15,16] Cases were evaluated as hypoglycemic when BGLs were below 60 mg/dL and normoglycemic when BGLs were 60 mg/dL or higher.[17] The amount of BB received by the cases was rated according to the specific toxic dose of each drug. The percentage of exposure was calculated one by one according to how much of the toxic dose was exposed. This value is termed as the "percentage of toxic dose" (PTD), and the table below lists the accepted toxic doses of the drugs (Table 1).

Statistical analysis

When the acceptable margin of error was set at 1.5%, a minimal sample size at 80% power was determined to be 108 cases. Statistical analysis was performed using the IBM SPSS version 22.0 software (IBM Corp., Armonk, NY, USA). Continuous variables were expressed in mean ± standard deviation (SD) or median (min-max), while categorical variables were expressed in number and

Table 1
Toxic doses and half-lives of some beta-blocker agents for childhood[27]

Beta-blockers	Toxic dose	Half-life (hours)
Metoprolol (mg/kg)	2.5	4-20
Propranolol (mg/kg)	4	3-4
Atenolol (mg/kg)	2	6-9
Bisoprolol (mg/kg)	10	9-12
Betaksolol (mg) (for adults)	20	14-24
Acebutolol (mg/kg)	12	3-4
Sotalol (mg/kg)	4-10	12

Table 2
Age and sex characteristics of groups and beta-blocker drugs to which they were exposed

	n	%	Mean±SD	Min-Max
Age (year)			11.6±5.7	2-17
Sex				
Female	83	61		
Male	53	39		
Drugs exposed to				
Metoprolol	39	28.7		
Propranolol	49	36		
Atenolol	11	8.1		
Bisoprolol	12	8.8		
Betaxolol	13	9.6		
Acebutolol	8	5.9		
Sotalol	4	2.9		

SD: Standard deviation.

frequency. The chi-square test was used to compare categorical data, and the Fisher exact test was used when the chi-square assumptions could not be provided. The t-test was applied to compare numerical variables. The Pearson correlation analysis was carried out to investigate the relationships between numerical variables. Logistic regression modelling was performed to predict the risk factors for the development of hypoglycemia; the forward stepwise technique was used. A p value of <0.05 was considered statistically significant.

RESULTS

The BB drug patients were exposed to were propranolol (36%), metoprolol (28.7%), betaxolol (9.6%), bisoprolol (8.1%), acebutolol (5.9%), and sotalol (2.9%). The mean SBP was 86.2±12 (range, 57 to 140) mmHg, the mean HR was 72.9±12.2 (range, 56 to 110) bpm, and the mean BGL was 104.4±42.8 (range, 42 to 200) mg/dL (Table 2).

Based on the mean values of the SBP, HR, and BGL of female and male cases at the time of admission, the mean SBP of females was 85.3±8.6 mmHg, the mean HR was 75.5±13.1 bpm, and the mean BGL was 89.7±20.4 mg/dL. Among males, the mean SBP was 87.7±15 mmHg, the mean HR was 68.5±8.9 bpm, and the mean BGL was 127.5±56.7 mg/dL (p=0.03, p=0.04, p<0.01, respectively) (Table 3). The calculated PTD in male cases was significantly higher than in female cases (p=0.01).

Considering the normal values of the patients according to their age, their blood pressure values were hypotensive or not one by one. Accordingly, 57 (41.9%) cases were hypotensive and 79 (58.1%) cases were normotensive. Seven (12.3%) cases in the

Table 3
Distribution of heart rate, systolic blood pressure, and blood sugar levels by age and sex

	Female (n=83)	Male (n=53)			
	Mean±SD	Mean±SD		p	t
Systolic blood pressure (mmHg)	85.3±8.6	87.7±15		0.03	1.6
Heart rate (/min)	75.5±13.1	68.5±8.9		0.01	4.2
Blood glucose level (mg/dL)	89.7±20.4	127.5±56.7		<0.01	5.5
Percentage of toxic dose (%)	161.9±47	171.1±67.3		0.01	-0.9
	≤6 years (n=48)	>6 years (n=88)			
	Mean±SD	Mean±SD	Min-Max	p	t
Systolic blood pressure (mmHg)	84.6±8.6	87.1±13.4		0.04	1.1
Heart rate (/min)	78.6±14	69.8±9.1		<0.01	4.8
Blood glucose level (mg/dL)	79.3±18.4	118.2±46		<0.01	5.6
Percentage of toxic dose (%)	155.1±2.1	171.1±32		0.7	-1.6
Blood glucose level (mg/dL) (whole group)	104.4±42.8		49-200		
Heart rate (/min) (whole group)	72.9±12.2		56-110		
Sistolik blood pressure- (mmHg) (whole group)	86.2±12		57-140		

SD: Standard deviation.

Table 4
Distribution of bradycardia and hypotension status of cases in groups by age and sex

	Hypotensive cases (n=57), (100%)		Normotensive cases (n=79), (100%)			Bradycardic cases (n=41), (100%)		Normocardic cases (n=95), (100%)		
	n	%	n	%	*p*	n	%	n	%	*p*
≤6 years (n=48)	7	12.3	41	51.9	<0.01	24	58.5	24	25.2	<0.01
>6 years (n=88)	50	87.7	38	48.1		17	41.5	71	74.7	
Female (n=83)	26	45.6	57	72.2	0.03	25	61	58	61.1	0.5
Male (n=53)	31	54.4	22	27.8		16	39	37	38.9	

hypotensive group were under the age of six, and 26 (45.6%) cases in the hypotensive group were female. Forty-one (51.9%) cases in the normotensive group were under the age of six, and 57 (72.2%) cases in the normotensive group were girls. Although the mean SBP was higher in the cases over six years old, the number and rate of individuals exceeding the hypotension limit were found to be significantly higher in the cases over six years old (Table 4). The mean of the PTD was determined to be higher in the cases older than six years than in the younger cases (p=0.7).

The cases were evaluated according to the normal values for their ages, whether the patients were bradycardic or not. Accordingly, bradycardia was detected in 41 (30%) cases. Twenty-four (58.5%) of these 41 cases were under the age of 6 and 25 (61%) cases were girls. While the mean HR value was higher in patients younger than six years, the rate of bradycardia was significantly lower. No relationship was found between bradycardia and sex (Table 4).

When bradycardia status and hypotensive status were compared, normal SBP (78%) was found to be significantly higher in the bradycardic group. Hypotension was detected in 51.6% of those with normal HR. Eight cases were found to be both bradycardic and hypotensive (5.8% of the whole group). The rate of normal HR (86%) was significantly higher in the hypotensive group (p=0.01) (Table 5).

When the relationship between the HRs, SBPs, and BGLs of the cases was examined, a positive poor correlation was found between BGL and HR (r=0.32, p<0.01). No linear correlation was found between BGL and SBP or between BGL and PTD (r=0.23, p=0.06 and r=0.16, p=0.05). A very strong negative correlation was found between PTD-SBP and PTD-HR (r=-0.90, p<0.01 and r=-0.76, p=0.04). A positive poor correlation was found between HR and SBP (r=0.42, p=0.09) (Table 6).

Hypoglycemia was detected in 11 cases (8.1% of the whole group). Five of these cases received acebutolol, three received metoprolol, and three received propranolol. When these cases were examined, the rate of bradycardia in hypoglycemic cases was found to be significantly lower (9.8%) than the rate of bradycardia in normoglycemics (p=0.01). The hypotension rate in hypoglycemic cases was found to be significantly lower (7%) than in normoglycemics (p=0.03) (Table 7).

We used the parameters of age, sex, PTD, SBP, and HR levels that had significant values in the binary analyses for the logistic regression model to examine

Table 5
Relationship between bradycardia and hypotension status of the cases in the group

	Normocardic cases		Bradycardic cases		
	n	%	n	%	*p*
Normotensive cases	46	48.2	33	78	
Hypotensive cases	49	51.6	8	22	0.01
Total	95	100	41	100	

Table 6
Correlation analysis between heart rate, systolic blood pressure, and blood sugar levels

	R	*p*
BGL-HR	0.32	<0.01
BGL-SBP	0.23	0.06
BGL-PTD	0.16	0.05
PTD-SBP	-0.90	<0.01
PTD-HR	-0.76	0.04
HR-SBP	-0.42	0.09

BGL: Blood glucose level; HR: Heart rate; SBP: Systolic blood pressure; PTD: Percentage of toxic dose.

the factors that may cause hypoglycemia. According to the results of this model, being younger than six years increased the development of hypoglycemia by 2.99 folds, by 3.6 folds, and an increase in PTD increased the development of hypoglycemia by 1.04 folds (Table 8).

In our study, none of the cases died due to either cardiovascular causes or hypoglycemia.

DISCUSSION

The primary objective of our study was to determine the predictive factors for the development of hypoglycemia in cases with BB intoxication. We found a correlation between decreased HR and decreased BGL. In addition, younger age, female sex, and a higher dose of the drug taken facilitated the development of hypoglycemia. However, bradycardia and hypotension were not seen more frequently in cases with hypoglycemia.

The secondary objective of our study was to determine how HR and SBP were affected in cases with BB intoxication. In male cases, while the mean HR was lower, the mean SBP was higher than the female cases. Additionally, the mean HR was lower in those older than six years, while the mean SBP was higher. As the amount of medication taken increased, the mean HR and SBP decreased.

Among the consequences that occur in cases of BB intoxication, those related to the CVS are the most important. Morbidity is dependent on bradycardia

Table 7
Relationship between hypoglycemia-bradycardia and hypoglycemia-hypotension

	Normoglicemic cases		Hypoglicemic cases		
	n	%	n	%	*p*
Normocardic cases	88	70.4	7	63.6	
Bradycardic cases	37	29.6	4	36.4	0.01
Total	125	100	11	100	
Normotensive cases	72	57.6	7	63.6	
Hypotensive cases	53	42.4	4	36.4	0.03
Total	125	100	11	100	

Table 8
Logistic regression model created for the development of hypoglycemia

	B	S.E.	OR	95% Cl for Exp B	*p*
Age	1.09	0.36	2.99	1.4-6.06	0.02
Sex	12.7	4.3	3.6	7.06-18.5	0.03
Percentage of toxic dose	0.04	0.19	1.04	1.02-1.08	0.04
Systolic blood pressure	-0.5	0.92	0.55	0.09-3.4	0.5
Heart rate	0.8	1.1	2.33	0.2-20	0.4
Constant	-19.9	6.1	0.1	0.2-20	0.01

-2 loglikehood=44,496.

and/or hypotension. One of the studies on this subject was conducted by Love et al.[10] In this study, 280 BB poisoning cases were examined, and cardiotoxicity was found in 41 (15%) cases. Four (1.4%) of these 41 cases died, and these cases were additionally exposed to a different drug. In our study, no exitus cases were detected. The reason for this may be that those who used another drug were excluded from our study. Similarly, in a study conducted by Belson et al.,[18] BB-linked cardiotoxicity was found in 1.6% of the cases. This low rate of cardiotoxicity can be explained by how, in this study, 83% of the cases came from exposure to only a single tablet. In this study group, 272 of 280 patients were discharged without any problems, four were reported to have minor and four to have moderate effects. In childhood, BB agents are considered toxic, even for those taking a single tablet. It is undeniable that the toxicity potential increases if the number of drugs increases. In a study by Langemeijer et al.,[19] myocardial depression increased as the dose of BB increased. In our study, the term PTD was developed to calculate how much the drug taken exceeds the determined dose, how much the HR increases, and how much the SBP decreases at that rate.

In our previous study, our team compared the BGLs of patients who received BB with those of patients who took a selective serotonin receptor inhibitor (SSRI).[20] The purpose of using SSRIs was that these drugs usually do not cause hypoglycemia. It was shown that BB intoxication decreased BGLs compared to other poisoning instances, but these values were not serious hypoglycemic events. Based on this result, in the current study, we attempted to examine which characteristics of patients with BB poisoning might be risk factors for the development of hypoglycemia. We found a correlation between the decrease in HR and BGL. In addition, we found that younger age, female sex, and a high dose of the drug used facilitated the development of hypoglycemia. However, since there is no similar study in the literature, we could not find an opportunity to compare our results.

According to BB poisoning cases in terms of age and sex, in a study conducted by Love et al.,[4] 208 children with BB poisoning were examined and they found that 57% of the cases were under four years old and 57% of them were males.

In many studies about poisoning, boys are exposed to toxic agents at a younger age and girls in the adolescent ages.[21] According to a study conducted by Lauterbach et al.,[22] 59% of 2,967 cases with BB poisoning were found to be female in the adult age group. In our study, 64.7% of the cases were over six years old and 61% of them were females. We believe that the reason for identifying such a high number of female cases is that we included adolescents in our study group.

According to the relationship between age and cardiac function, at younger ages, toxins are more destructive to cardiac functions.[23] In our study, although the mean HR value was higher in patients younger than six years old, the rate of bradycardia was higher. This may be due to the increased sensitivity to bradycardia when the age gets younger. This is also why SBP is lower in those younger than six years old. However, the fact that the number of cases exceeding the hypotension limit is higher in those over six years of age can be explained by the higher amount of drugs taken in the older age group (where the percentage of the toxic dose is higher than in the younger ones). Besides, BB agents show their cardiac effects through ß1-receptors first and they show vascular effects later.[24]

When we investigated which BBs were seen most frequently in cases of BB poisoning, the most common three BBs were atenolol, metoprolol, and propranolol in Love et al.'s studies.[4,6] Similarly, in our study, the most common poisoning agents were propranolol and metoprolol. Even in Love et al.'s[10] study conducted in 2000, propranolol (43.2%) was found to be the most common BB, as in this study.

When we examine the pathological conditions that occur in cases poisoned with BB, Love et al.[4] found that bradycardia was detected only in a two-year-old patient who received 50 mg of atenolol out of 208 children who were followed in their study, and this case was resolved without any treatment. In the same study, in one case, BGL was determined to be 55 mg/dL, and in other cases, hypoglycemia was not observed. In a study by Litovitz et al.,[25] a seven-year-old girl presented with hypotension, hypoglycemia, aspiration, and asystole after propranolol intake.

In a study conducted by Eibs et al.,[26] out of 49 children who received BBs, 30 (61.2%) had bradycardia and/or hypotension as CVS effects. In addition to CVS effects, hypoglycemia was observed in 12 children. Most of the cases that developed hypoglycemia received propranolol.

Similarly, 90 (66.1%) patients had cardiovascular effects (hypotension and/or bradycardia) in our study. There are publications in the literature showing that children who develop hypoglycemia are mostly exposed to agents with high lipophilicity, such as propranolol, or high membrane-stabilizing activity (MSA), such as acebutolol.[9,10] In our study, cases who developed hypoglycemia were exposed to either high-MSA or high-liposolubility drugs, such as acebutolol, metoprolol, and propranolol.

In the literature, hypoglycemia associated with BB intoxication has been linked to prolonged fasting in non-diabetic cases.[21] In our previous study, our team compared the BGLs of 40 cases who received BBs and 40 cases who received SSRIs. There was no low BGL at the time of the first admission in the BB group, but BGL was significantly lower at 1 and 24 h of follow-up than in the SSRI group.[20] However, based on the cases that exceeded the hypoglycemia limit, there was no significant difference. These data suggest that, as in the literature, the low BGL might have been due to prolonged fasting, not drugs.

Based on the mortality of BB intoxication, Love et al.[6] examined 10-year poison control service reports and did not see any deaths under the age of six in 19,388 cases of BB intoxication. In Langemeijer et al.'s[20] study, they did not observe any exitus in the same age group. Similarly, there was no mortality in our study.

The limitation of our study is that the number of cases, particularly the number of cases developing hypoglycemia, is low. If there were more cases of hypoglycemia, it would be easier to evaluate risk factors. Our study was established with a retrospective design, as it aimed to investigate the risk factors of a result. However, in light of these data, in a prospective study in which patients with BB poisoning may have been monitored for a longer period, the late effects of BB may have been detected. Moreover, knowing the nutritional status of the cases and body mass indexes would contribute to eliminating the confounding factors that may cause hypoglycemia. However, our study would still contribute to the literature, since it is the first study of this subject focusing on childhood.

In conclusion, in our study, patients who were younger, who took a large amount of drugs, and whose HRs were lower were at a greater risk of developing hypoglycemia. Therefore, cases of BB poisoning with these characteristics should be monitored more closely for BGL.

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REFERENCES

1. Yorulmaz A, Akbulut H, Yahya İ, Aktaş R, Emiroğlu HH, Peru H. Çocuk acil servisine zehirlenme nedeni ile başvuran olguların geriye dönük olarak değerlendirilmesi. J Pediatr Emerg Intensive Care Med 2017;4:96-103.
2. Khudair IF, Jassim Z, Hanssens Y, Alsaad WA. Characteristics and determinants of adult patients with acute poisoning attending the accident and emergency department of a teaching hospital in Qatar. Hum Exp Toxicol 2013;32:921-9.
3. Bucak İH, Turgut M, Tümgör G, Eynallı A. Çukurova bölgesinde üçüncü basamak bir hastanede 2006-2010 yılları arasında çocukluk çağı ilaç zehirlenmelerinin değerlendirilmesi. Türkiye Çocuk Hast Derg 2015;2:124-30.
4. Love JN, Howell JM, Klein-Schwartz W, Litovitz TL. Lack of toxicity from pediatric beta-blocker exposures. Hum Exp Toxicol 2006;25:341-6.
5. Veltri JC, Litovitz TL. 1983 annual report of the American Association of Poison Control Centers National Data Collection System. Am J Emerg Med 1984;2:420-43.
6. Love JN, Litovitz TL, Howell JM, Clancy C. Characterization of fatal beta blocker ingestion: A review of the American Association of Poison Control Centers data from 1985 to 1995. J Toxicol Clin Toxicol 1997;35:353-9.
7. Bronstein AC, Spyker DA, Cantilena LR Jr, Green J, Rumack BH, Heard SE. 2006 annual report of the American Association of Poison Control Centers' National Poison Data System (NPDS). Clin Toxicol (Phila) 2007;45:815-917.
8. Artman M, Grayson M, Boerth RC. Propranolol in children: Safety-toxicity. Pediatrics 1982;70:30-1.
9. Samuels TL, Uncles DR, Willers JW, Monteiro R, Halloran C. Logging the potential for intravenous lipid emulsion in propranolol and other lipophilic drug overdoses. Anaesthesia 2011;66:221-2.
10. Love JN, Howell JM, Litovitz TL, Klein-Schwartz W. Acute beta blocker overdose: Factors associated with the development of cardiovascular morbidity. J Toxicol Clin Toxicol 2000;38:275-81.
11. Reith DM, Dawson AH, Epid D, Whyte IM, Buckley NA, Sayer GP. Relative toxicity of beta blockers in overdose. J Toxicol Clin Toxicol 1996;34:273-8.
12. Love JN. Beta blocker toxicity after overdose: when do symptoms develop in adults? J Emerg Med 1994;6:799-802.
13. Abramson EA, Arky RA, Woeber KA. Effects of propranolol on the hormonal and metabolic responses to insulin-induced hypoglycaemia. Lancet 1966;2:1386-8.

14. Cryer PE. Diverse causes of hypoglycemia-associated autonomic failure in diabetes. N Engl J Med 2004;350:2272-9.
15. Craig-Brangan KJ, Day MP. Update: 2017/2018 AHA BLS, ACLS, and PALS guidelines. Nursing 2019;49:46-9.
16. Söğütlü Y, Biçer S. Çocuklarda ileri yaşam desteği konusundaki son öneriler: Amerikan Kalp Cemiyeti 2015 rehberindeki güncellemelerin incelenmesi. J Pediatr Emerg Intensive Care Med 2016;3:110-20.
17. Wolfsdorf JI, Glaser N, Agus M, Fritsch M, Hanas R, Rewers A, et al. ISPAD Clinical Practice Consensus Guidelines 2018: Diabetic ketoacidosis and the hyperglycemic hyperosmolar state. Pediatr Diabetes 2018;19 Suppl 27:155-77.
18. Belson MG, Sullivan K, Geller RJ. Beta-adrenergic antagonist exposures in children. Vet Hum Toxicol 2001;43:361-5.
19. Langemeijer JJ, de Wildt DJ, de Groot G, Sangster B. Intoxication with beta-sympathicolytics. Neth J Med 1992;40:308-15.
20. Gokalp G, Nalbant T, Berksoy E, Bardak S, Demir G, Demir S, et al. Is hypoglycemia really observed in pediatric beta-blocker intoxications? A case-control study. Arch Pediatr 2022;29:56-60.
21. Gokalp G. Evaluation of poisoning cases admitted to pediatric emergency department. Int J Pediatr Adolesc Med 2019;6:109-14.
22. Lauterbach M, Solak E, Kaes J, Wiechelt J, Von Mach MA, Weilemann LS. Epidemiology of hydrogen phosphide exposures in humans reported to the poison center in Mainz, Germany, 1983-2003. Clin Toxicol (Phila) 2005;43:575-81.
23. Qasqas SA, McPherson C, Frishman WH, Elkayam U. Cardiovascular pharmacotherapeutic considerations during pregnancy and lactation. Cardiol Rev 2004;12:240-61.
24. Vucinić S, Joksović D, Jovanović D, Vucinić Z, Todorović V. Factors influencing the degree and outcome of acute beta-blockers poisoning. Vojnosanit Pregl 2000;57:619-23.
25. Litovitz TL, Schmitz BF, Matyunas N, Martin TG. 1987 annual report of the American Association of Poison Control Centers National Data Collection System. Am J Emerg Med 1988;6:479-515.
26. Eibs HG, Oberdisse U, Brambach U. Intoxication with beta-receptor blockers (author's transl). Dtsch Med Wochenschr 1982;107:1139-43. German.
27. Shepherd G. Treatment of poisoning caused by beta-adrenergic and calcium-channel blockers. Am J Health Syst Pharm 2006;63:1828-35.