ORIGINAL ARTICLE

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Received: 28.01.2017
Acceptance:07.03.2017
DOI: 10.18521/ktd.288416

Konuralp Tıp Dergisi
e-ISSN1309–3878
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Evaluation of Cases Followed and Treated Due to Valproic Acid Intoxication In Child Emergency Outpatient Clinic Between 2010 and 2016

ABSTRACT

Objective: Our aim was to determine prognostic factors effecting clinical course of the patients referring to the Child Emergency Service in our hospital with valproic acid (VPA) poisoning.
Methods: Patients who had VPA poisoning diagnoses between 2010 and 2016 in our Child Emergency Service were retrospectively examined. Demographical characteristics, clinical findings, laboratory results, treatment methods and effective factors for prognosis were evaluated for the patients.
Results: The study were included 114 patients whose avarage age is 9.91±4.69 years Sixty-six of the patients were female and forty-eight were male. The most common reason for inclusion has been overdosing (100 patients, 87.72%). Fourteen patients (12.28%) had pure VPA poisoning. VPA serum level median value was 141.80 µ/mL (min-max; 102.20 – 640.38 µ/mL). Central nervous system depression was the most common clinical finding (six patients, 5.2%). Thrombocytopenia was detected in sixteen patients (14.0%) and hyperammoniemia in eighteen patients (15.8%). Average follow-up duration for the patients was 16.14 hours. L-carnitine treatment was applied for six patients (5.3%).
Conclusions: In long-term VPA usage, the importance of thrombocytopenia and ammonia level should not be forgotten during prognosis. Supportive treatment still maintains its importance in VPA intoxication and intensive care follow-up and treatment was necessary for two patients in our study and L carnitine was started for patients with suitable indications and preserves its importance in treatment.

Keywords: Valproic acid, poisoning, child emergency

2010–2016 yılları arasında çocuk acil polikliniğinde valproik asit intoksikasyonu nedeniyle takip ve tedavi edilen olguların değerlendirilmesi

ÖZET

Amaç: Çocuk Acil Servisimize valproik asit(VPA) zehirlenmesi tanısı ile başvuran hastaların klinik seyrini etkileyen prognostik faktörlerin belirlenmesi amaçlanmıştır.
Yöntem: Çocuk Acil Servisimize 2010-2016 yılları arasında VPA zehirlenme tanısı alan hastalar geriye dönük incelendi. Hastaların, demografik özellikleri, klinik bulguları, laboratuar sonuçları, tedavi yöntemleri ve prognozda etkili faktörler değerlendirildi.
Bulgular: Çalışmaya 114 hasta dahil edildi. Hastaların yaş ortalaması 9,91±4,69 yıl idi. Hastaların 66'sı kız ve 48'i erkekti. Alım nedenleri arasında en sık neden doz aşımı (100 hasta, %87,72) idi. 14 hasta (%12,28) ise suisidal saf VPA zehirlenmesi idi. VPA serum düzeyi ortanca değeri 141,80 µ/mL (min-max; 102,20 – 640,38 µ/mL) idi. En sık klinik bulgu (6 hasta, %5,2) santral sinir sistemi depresyonu mevcuttu. On altı hastada (%14,0) trombostopeni ve 18 hastada (%15,8) hiperamonyemi tespit edildi. Hastaların ortalama takip süresi 16,14 saat idi. Altı hastaya (% 5,3) L-karnitin tedavisi uygulandı.
Sonuç: Uzun dönem VPA kullanımında trombositopeni ve amonyak seviyesininde prognozdaki yeri unutulmamalıdır**.** VPA intoksikasyonunda destekleyici tedavi halen önemini korumakta olup çalışmamızda 2 hastamızda yoğun bakım takip ve tedavisi gerekmiş olup, L carnitin uygun endikasyonlu hastalara başlandı ve tedavide yerini korumaktadır.

Anahtar Kelimeler: Valproik asit, zehirlenme, çocuk acil

INTRODUCTION

Yearly incidence of childhood poisoning in developed countries is between 0.02 and 0.93%. Poisoned patients referring to Child Emergency Service constitute nearly 0.5-2% of all referrals in Turkey (1). Antiepileptic medicine poisonings have a significant place among poisoned patients. Their prevalence among the poisoned patients referring to child emergency services made change between 0.09-10% in the studies. (2-6)

Valproic acid (2-propylpentanoic acid, VPA) is one of the most commonly used antiepileptic agents during childhood (7). VPA poisonings in childhood frequently develop due to overdosing or suicidal use. Central nervous system (CNS) depression, cerebral edema, hyperammoniemia, hepatotoxicity, hemorrhagic pancreatitis, bone marrow suppression and death are among the clinical findings it causes (8-11). Treatment is supportive in valproic acid poisoning. In some special cases, L-carnitine, naloxone and hemodialysis are among other treatment options (12).

Its efficiency and increased usage ratios have lead to increase in VPA-related poisoning ratios. Publications on these poisoned patients the prevalence of whom increases gradually during childhood are presented in literature under the title "patient-based and other antiepileptic poisonings (12-14). Number of studies reported in adult age group is rather low (15).

Childhood VPA poisonings were examined under a single title in this study and clinical and demographical characteristics of the patients were tried to be detected and the factors playing a role in prognosis were examined.

MATERIAL AND METHOD

Files of patients followed up after VPA poisoning diagnosis in Child Emergency Service between January 2010 and January 2016 were retrospectively examined and evaluated in this research. The ethical approval was taken from Ondokuz Mayıs University Ethic Board on 15.4.2016 with 2016/159 decision number. Patients with VPA in toxication level (> 100 µ/ml) were included in the study. 30 patients whose serum levels were considered to be detected high since serum level couldn't be checked in due time range were excluded from the study (Figure 1).

In cases known to have more than one poisoning factor and/or suspected cases, only patients considered to have pure VPA poisoning were included in the study since the patient clinics and progressions could be affected. Inclusion and exclusion criteria mentioned in the studies are summarized in Figure 1.

Demographical characteristics, clinical findings, laboratory results, treatment methods, clinical courses and factors considered to be effective in prognosis were evaluated for the patients included in the study.

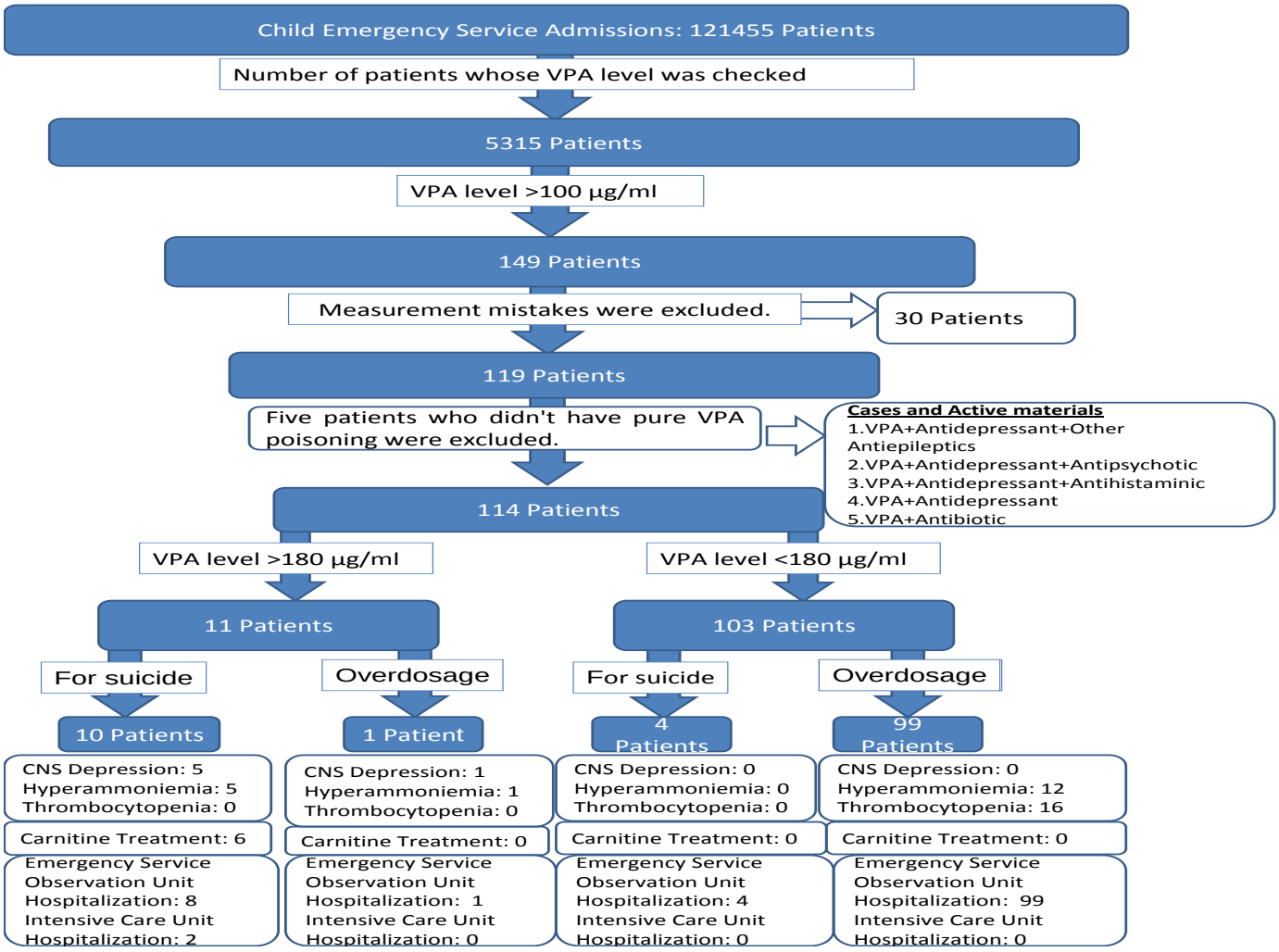

Figure 1. Selecting patient groups and their numeric distribution according to parameters

Statistical analysis

Statistical analyses of the research were made with SPSS 21.0 package program (IBM-SPSS Inc, Chicago, IL). Defining values for acquired data were calculated as numeric and percentage frequency, average±standard deviation and median. Chi-square test was used for the comparison of the groups for categorical characteristics and T-test for the difference between two independent averages in the comparison for the characteristics mentioned with measurement. Average of more than two groups was compared by variance analysis. $p<0.05$ was accepted as statistically significant.

RESULTS

Average age of the patients included in the study was 9.91±4.69 years. Sixty-six of the patients were female (57.9%) and forty-eight (42.1%) were male. Most of the patients were over five years of age. Referrals were mostly outpatients. Most of the patients were observed for 6 and 12 hours and again most of them were discharged from the emergency service after being observed in the emergency service. No statistically significant relation was found between the VPA level of the patient and accompanying disease, additional medicine use, form of the medicine taken and hospital arrival way among the factors investigated (Table 1).

Table 1. Comparison of VPA level and questioned factors

	n(total)	**Intoxication for Suicide** n(%)	**Overdose Intoxication** n(%)
Gender			
Male	48	4(8.3)	44(91.7)
Female	66	10(15.2)	56(84.8)
Age Groups			
0-2 years	5	0(0.0)	5(100.0)
2-5 years	17	0(0.0)	17(100.0)
5-12 years	48	1(2.1)	47(97.9)
12-18 years	44	13(29.5)	31(70.5)
Arrival way			
Outpatient	104	6(5.8)	98(94.2)
Transfer	10	8(80.0)	2(20.0)
Accompanying disease			
Present	106	7(6.6)	99(93.4)
Not present	8	7(87.5)	1(12.5)
Form of medicine taken			
Syrup	65	0(0.0)	65(100.0)
Tablet	48	14(29.2)	34(70.8)
Applied treatment methods			
IV fluid replacement	114	14 (12.8)	100 (87.2)
Stomach lavage	14	14 (100.0)	0 (0.0)
Activated charcoal	14	14 (100.0)	0 (0.0)
Carnitine treatment	6	5 (36.8)	1(0.00)
Hospitalization durations (hr)			
0-6	18	0 (0.0)	18 (100.0)
6.1-12	74	1 (1.4)	73 (98.6)
12.1-24	9	1 (11.1)	8 (88.9)
24	12	12 (100.0)	0 (0.0)
Clinical course			
Emergency Service Observance	113	14 (12.4)	99 (87.6)
Intensive Care Unit	2	2 (100.0)	0 (0.00)
Discharged from Emergency Service	111	11 (9.9)	100 (90.1)

Laboratory findings of the patients included in the study are shown in Table 2. Na and Cr values of the patients referring with intoxication for suicide were detected higher. A significant difference was not found in other laboratory findings.

Table 2. Average laboratory values checked

Biochemistry	n(total)	Intoxication for Suicide n (Avr. ± SD)	Overdose Intoxication n (Avr. ± SD)	p
Na (mEq/L)	78	14 (140.4±3.1)	64 (138.1±3.2)	**0.044**
K (mEq/L)	78	14 (4.1±0.5)	64 (4.3±0.4)	0.083
BUN (mg/dl)	84	14 (7.3±2.3)	70 (9.5±4.1)	0.505
Cr (mg/dl)	84	14 (0.6±0.2)	70 (0.4±0.2)	**0.035**
AST (U/L)	108	14 (17.2±4.7)	94 (26.2±16.7)	0.327
ALT (U/L)	108	14 (10.6±3.9)	94 (13.9±8.3)	0.295
D-Bilirubin (mg/dl)	55	12 (0.1±0.1)	43 (0.1±0.1)	0.149
ID-Bilirubin (mg/dl)	55	12 (0.3±0.4)	43 (0.2±0.0)	0.153
Troponin	4	3 (0.0±0.0)	1 (99.0±-)	0.135
CK-MB	4	4 (0.5±0.4)	0 (-)	-
Total Blood Count				
Leukocyte (10^3/µL)	108	14 (7125.4±1713.4)	94 (8270.2±3433.5)	0.476
Hemoglobin (g/dl)	108	14 (12.3±1.2)	94 (12.5±1.3)	0.334
Thrombocyte (10^3/µL)	108	14 (259.1x10^3±78.3 x10^3)	94 (225.1 x10^3±92.3x10^3)	0.281
Neutrophil (%)	108	14 (140.4±3.1)	64 (138.1±3.2)	0.421
Lymphocyte (%)	108	14 (34.4±10.2)	94 (35.4±13.7)	0.506
Coagulation parameters				
Prothrombin Time (sec)	28	12 (12.6±1.0)	16 (12.81±1.0)	0.662
INR (sec)	28	12 (1.1±0.9)	16 (1.15±1.0)	0.711
Serum Medicine Level				
Valproic acid (µg/mL)	114	14 (298.2±159.8)	100 (122.8±14.9)	0.124
Blood Gas				
pH	46	13 (7.4±0.3)	33 (7.4±0.5)	0.856
pO2 (mmHG)	46	13 (55.6±38.5)	33 (64.0±26.2)	0.431
pCO2 (mmHG)	46	13 (39.6±4.8)	33 (36.7±7.0)	0.645
HCO3 (mmol/L)	46	13 (22.7±1.9)	33 (21.6±2.7)	0.310
Ammonia (µg/dL)	53	11 (98.4±82.1)	42 (119.9±102.5)	0.397
Lactate (mg/dl)	32	11 (22.7±7.4)	21 (20.1±9.1)	0.390

While CNS depression was more frequent in patients with intoxication for suicide, thrombocytopenia and hyperammoniemia were more frequent in patients with overdosing intoxication (Table 3), complication development risk was higher over twelve years of age, again the complication risk was high in patients with overdose intoxication and high VPA level (Table 4).

Table 3. Vital findings and complication distributions of the patients

Complication	**Intoxication for Suicide n (%)**	**Overdose Intoxication n (%)**	**p**
CNS Depression	5 (80.0)	1 (20.0)	0.078
Thrombocytopenia	0 (0.0)	16 (100.0)	-
Hyperammoniemia	5 (27.8)	13 (72.2)	0.354
Total	14 (12.3)	100 (87.7)	
Vital findings*	**n=14(Avr. ± SD)**	**n=89 (Avr. ± SD)**	
Systolic TA (mmHG)	101.1±7.4	99.4±7.5	0.708
Diastolic TA (mmHG)	63.2±4.8	62.6±4.3	0.606
Pulse (/min)	94.4±20.9	88.9±15.4	0.094
Body Temperature (˚C)	36.3±0.3	36.5±0.3	0.469
Respiration Rate (/min)	23.0±3.1	25.6±3.9	0.372

* Unknown data for 11 patients.

Table 4. Statistical analysis of factors related with complication risk

	Complication						
	Present		Not present		OR	95% Cl	P
	n	Avr.±SD	n	Avr.±SD			
Age							
0-2	2	1.0±0.0	4	2.0±0.0	2.8	2.6-3.0	0.322
2-5	6	4.3±0.8	12	4.1±0.8	1.5	0.8-2.4	0.165
5-12	10	9.2±1.9	38	8.5±1.9	1.8	1.3-2.4	0.245
12-18	17	14.9±1.3	25	15.1±1.5	0.9	0.6-2.8	0.211
Total	35	10.7±4.8	79	9.5±4.6	0.9	0.7-3.1	0.491
VPA level (µg/mL)	35	173.1±114.9	79	127.9±31.3	28.7	17.5-72.6	**<0,001**
	n	**%**	**n**	**%**	**OR**	**95% Cl**	**P**
Gender							
Male	16	45.7	32	40.5	1.1	0.7-1.7	0.603
Female	19	54.3	47	59.5	0.9	0.6-1.3	0.754
Cause for high VPA							
Suicide	8	22.9	6	7.6	3.0	1.1-8.0	**0.022**
Overdosing	27	77.1	73	92.4	0.8	0.6-1.0	**0.048**
Form of medicine							
Syrup	16	45.7	49	62.0	0.7	0.5-1.1	0.105
Tablet	19	54.3	30	38.0	1.4	0.9-2.2	0.080
Presence of accompanying disease	32	91.4	74	93.7	99.0	10.6-921.3	0.666
Present	3	8.6	5	6.3	50.0	6.6-376.6	0.972
Not present							
Arrival way							
Outpatient	31	88.6	73	92.4	0.0	0.0-0.1	0.505
Transfer	4	11.4	6	7.6	0.2	0.2-0.8	0.758
Treatment method used							
Stomach lavage	8	16.0	6	6.9	1.2	0.9-1.8	0.510
IV fluid	34	68.0	75	86.2	1.0	1.0-1.1	0.596
Activated charcoal	8	16.0	6	6.9	0.9	0.8-1.2	0.398

Avr: Average, SD: Standard deviation, OR: Odds ratio, 95% Cl: 95% Confidence interval

DISCUSSION

VPA is a wide spectrum antiepileptic agent used most commonly around the world and it is a single-chain carboxylic acid (16). Due to its wide area of use and narrow theurapeutic treatment range, suicidal and accidental overdosings are frequent and constitutes one of the reasons for frequent emergency service referrals. Therapeutic serum concentration is between 50-100 µg/mL (17). Poisoning findings occur above these values. VPA level was above 100 µg/mL in our study and we evaluated the patients who referred to children emergency service.

Symptoms effecting different organ systems can be seen in VPA poisonings. Hypothermia, hypotension, tachycardia, high anion gap metabolic acidosis, hyperosmolarity, respiratory failure, rhabdomyolysis, acute kidney deficiency, acute kidney failure, methemoglobinemia, hyperammoniemia and hypofibrinogenemia are some of the metabolic effects observed (13). No significant metabolic effect was observed in some of our patients apart from hyperammoniemia. The presence of hyperammoniemia is also held responsible for stupor, coma and seizure occurrence. Coma and seizure were not observed in our patients. While limited toxicity is observed in patients with blood VPA level up to 450 µg/mL, coma presentation develops in those with a blood VPA level of 850 µg/mL and above.(9) Blood VPA level was above 450 µg/mL in two of our patients and we followed them under intensive care unit conditions and a significant toxicity presentation was not observed. The highest VPA level among our patients was 640,38 µg/mL, we did not come across any coma presentation.

CNS depression is observed when VPA level is 180 µg/mL or the medicine is taken more than 200mg/kg. Blood VPA levels of eleven patients in our study were above 180 µg/mL and CNS depression was observed in six of them.

Bone marrow depression is observed in vaproic acid poisoning, thrombocytopenia is observed especially in those with VPA level above 450 µg/mL. Mechanism of vaproic acid-related thrombocytopenia is not clear. Thrombocyte antibodies formed by VPA or its metabolytes cause peripheral thrombocyte destruction or dose-dependent bone marrow suppression (18). Sixteen of our patients in our study had thrombocytopenia during referral. Leucopenia was not observed in any of our patients. Bone marrow examination was not required.

Acute pancreatitis may also develop in high dose VPA use (19). The main mechanism in acute pancreatitis

developing due to VPA is the direct toxic effect of free radicals on pancreas tissue (20). Pancreatitis presentation was not observed in our patients.

Treatment of VPA toxication is mainly symptomatic. There is no specific antidote. Intravenous fluid treatment, stomach lavage in suicidal intakes and single dose active charcoal applications, L-carnitine treatment and hemodialysis applications for chosen cases are available. Stomach lavage and active charcoal were applied to the patients referring with suicidal poisoning in our study.

95% of Valproic acid effective through inhibition of voltage-dependent sodium channels and gamma aminobutyric acid (GABA) transaminase is metabolized through bilirubin uridine diphosphate glucuronosyl transferase enzyme in liver and oxidation. Carnitine is used during VPA oxidation.

Carbamoyl synthetase 1 is the enzyme responsible for adding ammonia in urea cycle. Carnitine is the activator of carbamoyl phosphate synthetase 1 activator and VPA is the inhibitor of the same enzyme. If carnitine is not adequate, carbamoyl synthetase 1 activation stops and ammonia cannot enter urea cycle (21, 22). It causes ammonia accumulation in plasma. L-carnitine is especially useful for decreasing high ammonia especially causing coma development. Using L-carnitine with a dose of 50-100 mg/kg for three days is recommended especially for hepatotoxicity, hyperamoniemia, CNS depression and high dose (400mg/kg) VPA intake (14,23,24). In our study, carnitine treatment was started only in six of the patients taking VPA for suicide.

Hemodialysis should be considered for the patients who have severe neurological and cardiological involvement and VPA level above 850µg/ml (14). We did not have any patients with a VPA level above 850µg/ml or any patients who have hemodialysis in our study.

Mechanic ventilation is applied in conditions where the preservation of airway is required such as patients with respiratory depression and brain edema. But mechanic ventilation was not required for our patients. Only two of our patients were followed-up in intensive care unit.

As a result, toxicity related to antiepileptic agent such as common VPA usage is frequent. In our study we came across complications such as CNS depression and thrombocytopenia. We shared probable complications, prognostic factors and treatment methods to lead the way of the doctors coming across VPA poisoning in children emergency service.

REFERENCES

1. Özayar E, Değerli S, Güleç H, ve ark. Yoğun bakıma kabul edilen zehirlenme olgularının retrospektif analizi. Yoğun Bakım Derg, 2011;3:59-62.
2. Sümer V, Güler E, Karanfil R, ve ark. Çocuk acil servisine başvuran zehirlenme olgularının geriye dönük olarak değerlendirilmesi. Turk Arch Ped. 2011;46:234-240.
3. Kondolot M, Akyıldız B, Görözen F, ve ark. Çocuk Acil Servisine getirilen zehirlenme olgularının değerlendirilmesi. Çocuk Sağlığı ve Hastalıkları Dergisi, 2009;52:68-74.
4. Türkmenoğlu Y, Gümüşoğlu Akşahin B, Sarıtaş Ü, ve ark. Çocukluk Çağı Zehirlenmelerine Yeniden Bakış Okmeydanı Tıp Dergisi, 2015:31(2):82-91.
5. Deniz T, Kandiş H, Saygun M, ve ark. Kırıkkale Üniversitesi Tıp Fakültesi Acil Servisine Başvuran Zehirlenme Olgularının Analizi. Düzce Tıp Dergisi, 2009;11(2):15-20.
6. Ayaz T, Bilir Ö, Ersunan G, ve ark. İntihar Amaçlı İlaç Zehirlenmelerinin Değerlendirilmesi. Konuralp Tıp Dergisi, 2015;7(1):53-56.
7. Chang R, Chou MC, Hung LY, et al. Study of Valproic Acid-Enhanced Hepatocyte Steatosis. BioMed Research International 2016, Article ID 9576503:11-http://dx.doi.org/10.1155/2016/9576503.
8. Lheureux PE, Hantson P. Carnitine in the treatment of valproic acid-induced toxicity.Clin Toxicol (Phila), 2009;47:101–11 .
9. Shadnia S, Amiri H, Hassanian-Moghaddam H, et al. Favorable results after conservative management of 316 valproate intoxicated patients.. J Res Med Sci. 2015;20(7):656–661. doi:10.4103/1735-1995.166211
10. Katiyar A, Aaron C. Case files of the children's hospital of Michigan regional poison control center: The use of carnitine for the management of acute valproic acid toxicity. J Med Toxicol. 2007;3:129–38.
11. Uluca Ü, Şen V, Karabel D, et al. Yoğun Bakıma Yatış Endikasyonlarının Önemli Bir Nedeni: Çocuk ve Adolesan Akut Zehirlenmeleri. Konuralp Tıp Dergisi, 2016;8(1):1-4.
12. Jung J, Eo E, Ahn KO Am A case of hemoperfusion and L-carnitine management in valproic acid overdose. J Emerg Med. 2008;26(3):388.e3-4.
13. Mindikoglu AL, King D, Magder LS, et al. Valproic Acid-Associated Acute Liver Failure in Children: J Pediatr. 2011;158(5):802–807. doi:10.1016/j.jpeds.2010.10.033.
14. Temel V, Arikan M, Temel G. High-flux hemodialysis and levocarnitine in the treatment of severe valproic Acid intoxication. Case Rep Emerg Med. 2013;20183:526469. doi: 10.1155/2013/526469.
15. Shadnia S, Amiri H, Hassanian-Moghaddam H, et al. Favorable results after conservative management of 316 valproate intoxicated patients. J Res Med Sci. 2015;20(7):656-61. doi: 10.4103/1735-1995.166211.

16. Saleh DA, Ismail MA, Ibrahim AM. “Non alcoholic fatty liver disease, insulin resistance, dyslipidemia and atherogenic ratios in epileptic children and adolescents on long term antiepileptic drug therapy,” Pakistan Journal of Biological Sciences, 2012;15(2):68–77
17. Akçay T (Çev. Eds). Nelson Pediatri. Nobel Tıp Kitabevi, İstanbul, 2015.
18. Nasreddine W, Beydoun A. Valproate-induced thrombocytopenia: a prospective monotherapy study. Epilepsia. 2008;49(3):438-45. Epub 2007 Nov 21.
19. Hurdle AC, Moss RD. Unrecognized valproic acid intoxication.Am J Emerg Med. 2009;27(2):250.e1-2. doi: 10.1016/j.ajem.2008.05.028.
20. Jones MR, Hall OM, Kaye AM, et al. Drug-induced acute pancreatitis: a review. Ochsner J. 2015;15(1):45-51.
21. Itoh H, Suzuki Y, Fujisaki K, et al. Correlation between plasma ammonia level and serum trough concentration of free valproic acid in patients with epilepsy.Biol Pharm Bull. 2012;35:971-4.
22. Janicki PK, Bezinover D, Postula M, et al. Increased Occurrence of Valproic Acid-Induced Hyperammonemia in Carriers of T1405N Polymorphism in Carbamoyl Phosphate Synthetase 1 Gene. ISRN Neurology. 2013;7.
23. Mock CM, Schwetschenau KH. Levocarnitine for valproic-acid-induced hyperammonemic encephalopathy. Am J Health Syst Pharm. 2012;69:35-9.
24. Perrott J, Murphy NG, Zed PJ. L-carnitine for acute valproic acid overdose: a systematic review of published cases. Ann Pharmacother. 2010;44:1287-93.