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Hemodialysis, Levocarnitine and Meropenem Application in the treatment of severe Valproic Acid-Induced Toxicity in the Intensive Care Unit

Yoğun Bakım Ünitesinde Valproik Asit Kaynaklı Ciddi Toksisite Tedavisinde Hemodiyaliz, Levokarnitin ve Meropenem Uygulaması

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ABSTRACT

Valproic acid (VPA) is currently a drug that can be used in the prophylaxis of epilepsy, bipolar disorder, schizoaffective disorder, schizophrenia and migraine. Valproic acid poisoning can result in central nervous system depression, shock, acute hyperammonemia, cerebral edema, coma and death. In this case, we wanted to present a patient who was treated with levocarnitine, hemodialysis and meropenem due to severe VPA toxicity. A 41-year-old male patient was firstly brought to the emergency room and then Intensive Care Unit with confusion. The patients was intubated because of his Glasgow Coma Score of 6 and respiratory failure. The patient had tachycardia, hypotension, and needed vasopressor medication. While liver function tests were found to be normal, hyperammonemia was thought to be drug-related. The patient's blood valproate level was 1055mg/L (therapeutic normal range: 50-100mg/L). The patient who developed aspiration pneumonia was given meropenem, which was found to be beneficial in valproic acid intoxication. Clinical manifestations of valproic acid poisoning are central nervous system depression, respiratory depression, hypotension, metabolic acidosis, bone marrow failure, brain edema, hypoglycemia, hypernatremia, and hyperammonemia. Treatment of acute valproic acid poisoning usually includes supportive care and fluid therapy, vasopressor support, electrolyte imbalance, and correction of acid-base disorders. Since the initial valproate level was 1055 uq/ml in our case, we applied to hemodialysis as the first treatment. We used levocarnitine especially because it can be useful in hyperammonemia. As a result, we observed that combined treatment of hemodialysis, levocarnitine and meropenem rapidly decreased the valproic acid level and resulted in a successful recovery.

Keywords: Valproic acid, Intoxication, Levocarnitine, Dialysis, Intensive Care.

ÖZET

Valproik asit (VPA) günümüzde epilepsi, bipolar bozukluk, şizoafektif bozukluk, şizofreni ve migren profilaksisinde kullanılabilen bir ilaçtır. Valproik asit zehirlenmesi merkezi sinir sistemi depresyonu, şok, akut hiperammonemi, beyin ödemi, koma ve ölümle sonuçlanabilir. Bu olguda şiddetli VPA toksisitesi nedeniyle levokarnitin, hemodiyaliz ve meropenem tedavisi uyguladığımız bir hastayı sunmak istedik. 41 yaşında erkek hasta önce acil servise sonrasında Yoğun Bakım Ünitesi'ne bilinç bulanıklığıyla getirildi. Glasgow Koma Skoru 6 ve solunumu yetersiz olduğu için entübe edildi. Hastanın taşikardisi, hipotansiyonu, vasopressor ilaç ihtiyacı vardı. Karaciğer fonksiyon testleri normal bulunurken, hiperammoneminin ilaca bağlı olduğu düşünüldü. Hastanın kan valproat düzeyi 1055mg/L (terapötik normal aralık: 50-100mg/L) bulundu. Aspirasyon Pnömonisi gelişen hastaya valproik asit intoksikasyonunda yararlı olduğu saptanan meropenem verildi. Valproik asit zehirlenmesinin klinik belirtileri, merkezi sinir sistemi depresyonu, solunum depresyonu, hipotansiyon, metabolik asidoz, kemik iliği yetmezliği, beyin ödemi, hipoglisemi, hipernatremi ve hiperamonyemidir. Akut valproik asit zehirlenmesinin tedavisi genellikle destekleyici tedavi ve sıvı tedavisi, vazopresör desteği, elektrolit dengesizliği ve asit-baz bozukluklarının düzeltilmesini içerir. Olgumuzda başlangıç valproat düzeyi 1055 uq/ml olduğu için ilk tedavi olarak hemodiyalize başvurduk. Levokarnitin özellikle hiperammonemide yararlı olabileceğinden kullandık. Sonuç olarak hemodiyaliz, levokarnitin ve meropenem kombine tedavisinin valproik asit düzeyini hızla düşürdüğü ve başarılı bir şekilde iyileşme sağladığını gözlemledik.

Anahtar Kelimeler: Valproik asit, İntoksikasyon, Levokarnitin, Diyaliz, Yoğun bakım.

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INTRODUCTION

Valproic acid (VPA) is a drug that can be used for prophylaxis of epilepsy, bipolar disorder, schizoaffective disorder, schizophrenia and migraine today.[1] Side effects related to VPA use are nausea, diarrhea, vomiting, pancreatitis, leukopenia, anemia, thrombocytopenia, hypofibrinogenemia, metabolic acidosis, hypernatremia, hypocalcemia, hypoglycemia, acute renal failure, hypothermia, hypotension and tachycardia.[2,3] Valproic acid intoxication may result in central nervous system depression, shock, acute hyperammonemia, brain edema, coma and death.[4] There is no specific antidote for valproate intoxication.[5] The treatment is supportive therapy. Traditional treatment methods have been defined as activated charcoal, levocarnitine and hemodialysis. Studies have shown that naloxone is useful in carbapenem antibiotics. However, none of them came to the fore as standard treatment.[6,7]

In this case report, we present a case in which we applied levocarnitine, hemodialysis and meropenem treatment due to severe VPA toxicity in the Intensive Care Unit.

CASE REPORT

A 41-year-old male patient with a diagnosis of schizophrenia and hypertension was brought to the emergency department and then in the Intensive Care Unit. When the patient admitted to the Emergency department, he was intubated because his Glasgow Coma Scale (GCS) was 6. There was no abnormality in the patient's vital signs, except for sinus tachycardia. Vasopressor support was provided to the patient who developed deep hypotension during the follow-up (norepinephrine 0.48 mcg/h). The patient's laboratory data are summarized in Table 1. He was found to be taking 50 g valproate. The patient's blood valproate level was found to be 1055 mg/L (therapeutic normal range: 50-100 mg/L). The change in the patient's valproate levels is shown in Figure 1. While liver function tests were normal, hyperammonemia was thought to be drug-related. No edema was detected in brain tomography. Activated charcoal treatment was not given to the patient whose medication time was uncertain. Due to hyperammonemia, 6 g bolus L-carnitine, was given as maintenance 9 g/day. Hemodialysis (HD) was taken 3 times until the valproate level fell below 100 mg/L. Every 6 hours, valproic acid, Artreial Blood Gases (AKG), Complete Blood Count (CBC), electrolyte, Liver Function Tests (LFT), ammonia, and ECG were monitored. The followed parameters of the patient are presented in Table 1. The patient who developed pneumonia due to aspiration was given meropenem, which was found to be beneficial in valproic acid intoxication. The patient's clinical improvement was extubated on the 5th day. The patient, whose general condition improved, was transferred to the psychiatry service.

Table 1. The followed parameters of the patient

Paramaters	**1 DAY**	**2 DAYS**	**3 DAYS**	**4 DAYS**	**5 DAYS**
Glucose (mg/dL)	129	119	162	128	261
Creatinine (mg/dL)	0.9	0.8	0.81	0.91	0.68
ALT (IU/L)	18	14	12	35	76
Sodium (mmol/L)	142	148	139	144	138
Potassium(mmol/L)	3.8	3.5	3.4	3.6	3.3
Amylase	171	155	65	49	75
pH	7.38	7.41	7.52	7.36	7.37
PCO_2 (mmHg)	36.6	41.1	32.5	36.4	32.7
PO_2 (mmHg)	103	159	164	147	93
O_2 support	mechanical ventilation	mechanical ventilation	mechanical ventilation	mechanical ventilation	extubated
Lactate(mmol/L)	14	17	12	7	8
HCO_3^- (mmol/L)	22.4	25.9	25.6	24.1	20.1
Leukocytes (10^3/µL)	6.25	7.8	11.4	10.23	6.96
Hemoglobin (g/dL)	15.6	13.1	12.5	11.3	10.8
Platelet(160x10^3uq/L)	160	153	79	64	108
Valproic Acid (mg/L)	1055	530	127	76	5
Ammonia	56	106	78	714	92
Need for vasopressors	+	-	-	-	-

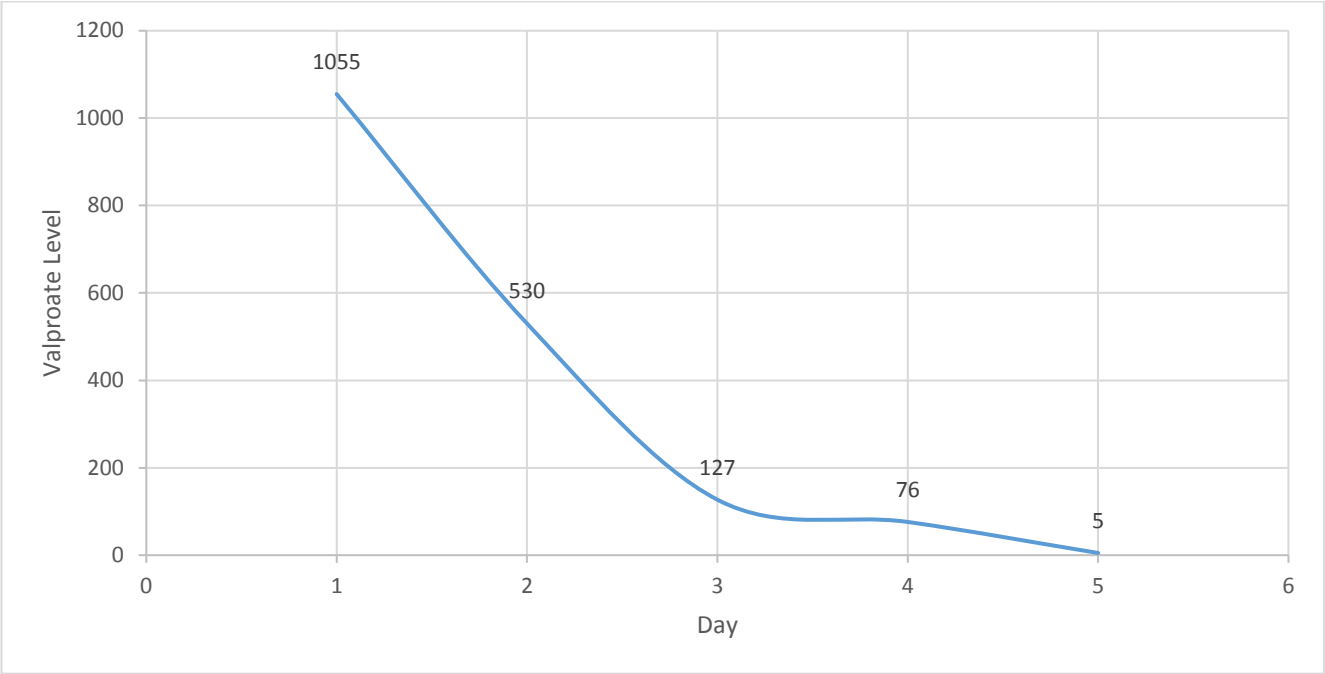

Figure 1. *The change in the patient's valproate levels.*+-

DISCUSSION

Valproic acid poisoning can manifest with various symptoms and is directly related to its plasma concentration. Serious poisonings usually occur above 850 uq/mL and can be life-threatening.[1] Clinical signs of valproic acid intoxication are central nervous system depression, respiratory depression, hypotension, metabolic acidosis, bone marrow failure, cerebral edema, hypoglycemia, hypernatremia, and hyperammonemia.[8] CNS depression usually plasma concentration 180 uq/mL It is observed when it exceeds. Thrombocytopenia is observed when the plasma concentration exceeds 450 uq/mL.[9] Our patient had central nervous system depression, respiratory depression, hypotension, thrombocytopenia, hypernatremia, and hyperammonemia. Activated charcoal treatment may be beneficial in early admissions. In our case, activated charcoal was not used because the drug intake time developed for 12 hours. Treatment of acute valproic acid intoxication usually includes supportive therapy and fluid therapy, vasopressor support, electrolyte imbalance, and correction of acid -base disorders. In addition, there may be a need for mechanical ventilation in consciousness disorders due to central nervous system depression or brain edema.[9] Levocarnitine may be especially useful in hyperammonemia. It is thought that the mechanism of action of levocarnitine may be effective in reducing the ammonia level and eliminating the coma picture. The recommended treatment dose of levocarnitine is 50-100 mg/kg/day.[10,11] Since our patient had hyperammonemia, recommended doses of levocarnitine were used.

Valproate level is above 850 uq/mL and severe neurological or cardiovascular symptoms are observeD.[12] Since the initial valproate level was 1055 uq/ml in our case, we applied to hemodialysis as the first treatment for the patient. After 3 sessions of hemodialysis, a significant decrease was found in serum valproate and ammonia levels.

Khobrani et al., were observed that the mental status of the patient improved despite the high ammonia level in which meropenem treatment was applied for aspiration pneumonia and valproate toxicity together with levocarnitine treatment.[13] Since our patient had aspiration pneumonia, meropenem antibiotherapy, which is known to be beneficial in valproate toxicity, was preferred as a treatment option. Figure 1 shows the decrease in valproic acid level after treatment.

CONCLUSION

As a result of the treatments, our patient was successfully extubated and discharged from the intensive care unit without any sequelae. As a result, it was observed that combined treatment of hemodialysis, levocarnitine and meropenem rapidly decreased the

valproic acid level and successfully treated the intoxication of it.

Authorship contribution statement

Consept and desing: CNDŞ, NY, HB, AE.

Acquisition of data: CNDŞ, NY, HB, AE.

Analysis and interpretation of data: CNDŞ, NY, HB, AE.

Drafting of the manuscript: AE.

Critical revision of the manuscript for important intellectual content: AE.

Supervision: AE.

Declaration of competing interest

None of the authors have potential conflicts of interest to be disclosed.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

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