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Acute Valproic Acid Intoxication: An Attempt at Estimating the Correlation Between Serum Level and Clinical Manifestations

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Abstract

We investigated the association between serum valproic acid (VPA) levels and clinical conditions in patients after acute intoxication with this drug. We performed a retrospective study of cases of VPA intoxications hospitalized in Toxicology Unit in Cracow in 2 years of observation. The study included 26 patients (age: 35.69 ± 12.93 years). In all patients, the VPA plasma level was higher than the therapeutic range, mean $\pm$ SD: 275.32 ± 135.97 $\mu\text{g/ml}$. About half of poisoned patients described in this report were treated with VPA prior to the poisoning. We noted four cases of mixed VPA intoxications with ethanol. Acute pulmonary failure was observed in two persons. The mean hospital stay for all patients was 4.69 days. This analysis demonstrates that increased serum VPA levels, in acute intoxication with this drug, were associated with the severity of poisoning — in PSS ($P = 0.019$) and in Matthews coma scale ($P = 0.022$), diastolic pressure ($P = 0.022$) and length of stay in hospital ($P = 0.001$). No correlation was detected between the serum VPA concentration and the heart rate and systolic blood pressure. In persons treated with VPA earlier, the course of poisoning was less severe, although these results were not statistically significant.

Keywords: valproic acid, acute intoxication, clinical manifestations, drug serum level, toxicity

1. Introduction

Valproic acid (VPA) (and its derivatives) is a commonly used conventional antiepileptic drugs (AED) for pharmacotherapy in epileptic patients. VPA was introduced in 1978 as AED [1]. Valproic acid is characterized by multidirectional action that involves increased gamma-aminobutyric acid (GABA)-ergic transmission, reduced release and/or effects of excitatory amino acids, blockage of voltage gated sodium channels and modulation of dopaminergic and serotonergic transmission [2]. This drug is effective in patients with all types of seizures, and especially in those with idiopathic generalized epilepsy [3, 4]. It is also prescribed to treat bipolar and schizoaffective disorders, social phobias and neuropathic pain, as well as for prophylaxis and treatment of migraine headache [5–9]. Valproic acid is a fatty acid which is about 90% bound to plasma proteins and the main metabolic transformations of valproic acid take place in liver, including that of the cytochrome P-450. Valproic acid follows a non-linear pharmacokinetic profile in terms of protein-binding saturation [10]. Acute VPA intoxication also occurs as a consequence of suicidal or accidental overdose. VPA intoxication incidence is increasing [11–14], probably because of its use in psychiatric disorders. It usually results in mild and self-limited central nervous system depression. However, serious toxicity and even deaths have been reported [15, 16]. The therapeutic serum concentrations for VPA are 50–100 µg/ml [17, 18]. Monitoring VPA serum levels helps to evaluate therapeutic response, compliance and possible toxicity.

2. Aim

The aim of study was to evaluate plasma concentrations of VPA and the clinical symptoms of acute intoxication.

3. Materials and methods

We performed a retrospective study of all cases of VPA intoxications ($n = 31$) hospitalized in Toxicology Unit in Cracow in 2 years of observation. A total of 26 patients who fulfilled inclusion and exclusion criteria were included in this study. The inclusion criteria were patients should be at least 18 years of age and documented serum VPA concentration should be ≥ 100 µg/ml. Patients taking VPA with other drugs which have an effect on VPA pharmacokinetic (i.e. carbamazepine, benzodiazepine, barbiturate) and patients with abnormal renal or liver function tests were excluded. From the medical records, relevant demographic data were taken, i.e. age and gender. The clinical spectrum consisted of consciousness disturbances, breath, heart rate, blood pressure, serum level of VPA, severity of poisoning, length of stay in hospital and treatment effect (survival/death). The project was reviewed and approved by the Ethics Committee, Medical University of Warsaw (no. AKBE/32/13).

The level of consciousness was graded on a scale of 0–IV according to Matthew and Lawson coma scale. Matthew-Lawson coma scale of determining severity of coma: grade 0—fully

conscious, alert; grade I—drowsy but responds to verbal command; grade II—unconscious patient but responds to minimal painful stimuli, reflexes intact; grade III—unconscious patient but responds to maximal painful stimuli, absence of superficial reflexes and sluggish deep reflexes; grade IV—unconscious patient with no response to painful stimuli, loss of all reflexes including corneal, laryngeal, pharyngeal. Grades III and IV are considered as severe grades of poisoning [19].

Severity of intoxication was classified according to Poisoning Severity Score (PSS). The PSS is a classification scheme for cases of poisoning in adults and children. The PSS grades severity as (0) none—no symptoms or signs related to poisoning, (1) minor—mild, transient and spontaneously resolving symptoms, (2) moderate—pronounced or prolonged symptoms, (3) severe—severe or life-threatening symptoms, and (4) fatal poisoning—death [20].

3.1. Statistical analysis

The data were collected in a Microsoft Excel database. Data are presented as mean and standard deviations. Statistical analysis of all data was performed by Statistica version 12 using the Pearson’s *r*, Spearman’s rho, Mann-Whitney *U* test. Differences were considered statistically significant at *P* < 0.05.

4. Results

We studied episodes of hospitalization for VPA intoxication in 26 patients, of whom 9 were men (34.61%). The mean age was 35.69 ± 12.93 years (range: 18–73 years) (Table 1).

Characteristics	N (%)
Gender	
Female	17 (65.39%)
Male	9 (34.61%)
Total	26 (100%)
Age, years	
Range: 18–73	
Mean ± SD: 35.69 ± 12.93	

Table 1. Demographics characteristics of study population.

Half of the poisoned patients (50%) described in this report were treated with valproic acid due to epilepsy or psychotic disorders prior to the poisoning. These patients had a less severe clinical course of poison, although these results were not statistically significant (*P* = 0.09).

The following intensity of quantitative consciousness disturbances according to Matthew’s scale was observed: grade 0—26.92%, I—26.92%, II—30.77%, and III—15.39%.

Parameters	
Systolic blood pressure (SBP), mmHg	
Range	100–160
Mean ± SD	127.15 ± 16.55
Diastolic blood pressure (DBP), mmHg	
Range	50–100
Mean ± SD	79.23 ± 12.25
Heart rate (HR), beats/min	
Range	58–122
Mean ± SD	88.46 ± 17.58
Breath	
Competence of a respiration	24 (92.31%)
Intubation	2 (7.69%)
Matthew coma scale (MCS)	
Grade 0	7 (26.92%)
Grade 1	7 (26.92%)
Grade 2	8 (30.77%)
Grade 3	4 (15.39%)
Grade 4	0 (0%)
Poisoning severity score (PSS)	
Minor	14 (53.85%)
Moderate	7 (26.92%)
Severe	5 (19.23%)
Ethanol, ‰	
Range	0–2.92
Mean ± SD	0.305 ± 0.77
Yes	4 (15.38%)
No	22 (84.62%)
Co-morbidity	
Depression	7 (26.92%)
Alcohol dependence syndrome	4 (15.38%)
Personality disorder	5 (19.23%)
Somatic disease	3 (11.54%)
Bipolar disorder	2 (7.69%)
Schizophrenia	4 (15.38%)
Other mental disorder	5 (19.23%)
Epilepsy	9 (34.62%)
Length of stay in hospital, days	
Range	2–13
Mean ± SD	4.69 ± 2.57
Treatment effect	
Discharged from hospital in good condition	17 (65.39%)
Discharged from hospital on a voluntary distractions	7 (26.92%)
Referral to mental hospital/ward	2 (7.69%)
Toxic valproic acid level, µg/ml	
Range	110–660
Mean ± SD	275.32 ± 135.97

Table 2. Clinical parameters distribution in examined population.

The serum VPA concentration showed moderate positive correlations with Matthew's scale (*Spearman's rho* = 0.45, $P = 0.022$).

The minimal and maximal values of blood pressure were: 100–160 and 50–100 mmHg, respectively, for systolic and diastolic blood pressure; heart rate: 58–122 beats/min; breathing rate in non-intubated patients: 13–20 breaths/min.

Correlational analysis (Pearson's r) revealed a moderate negative correlation between the VPA concentration and diastolic blood pressure ($r = -0.45$, $P = 0.022$). This negative correlation means that when the VPA level is higher, the diastolic blood pressure is lower.

In the study population, no statistical correlation was found between the serum VPA concentration and the heart rate ($r = -0.01$, $P = 0.944$), and systolic blood pressure ($r = -0.09$, $P = 0.655$).

Severity of intoxication was classified according to poisoning severity score (PSS). The PSS was minor in 14 patients, moderate in 7 patients and severe in 5 patients.

A positive relationship between the decrease in number of PSS and the increasing VPA serum level was demonstrated (*Spearman's rho* = 0.46, $P = 0.019$).

A significant proportion of patients had comorbid mental health disorders (e.g. depression, personality disorders, schizophrenia, and bipolar disorder).

Only two patients were inefficient to breathe and they required intubation. No patients had arrhythmias and seizures.

Alcohol was co-ingested by four patients. The mean ethanol concentration was 0.305‰.

The mean length of hospital stay was 4.69 days. We observed strong correlation between the serum level of VPA and the number of days of stay in hospital ($r = 0.96$; $P = 0.001$).

Seventeen of these 26 patients were discharged to home in good condition and two to a psychiatric ward. There were no reported mortalities among the cases of VPA intoxications.

The mean of serum level of valproic acid was 275.32 ± 135.97 µg/ml.

The characteristics of clinical parameters are shown in **Table 2**.

5. Discussion

Despite the fact that valproic acid is an old generation antiepileptic drug, in the literature, there is little information about the case series of VPA overdose. However, there is a description of case reports of VPA intoxication [21–24].

In our study, a positive relationship between the decrease in number of PSS and the increasing VPA serum level was demonstrated (*Spearman's rho* = 0.46, $P = 0.019$). It has been observed that the higher the concentration of VPA, the more severe the poisoning. In the literature, a serum level of >450 µg/ml was more likely to be associated with a moderate or major adverse outcome ($P < 0.005$) [11].

Symptoms of VPA intoxication are diverse. The most common manifestation of overdose is central nervous system (CNS) depression [25, 26]. Other studies show that some patients have mild to moderate lethargy [13, 27]. It was noted that patients who ingest more than 200 mg/kg VPA and/or have plasma concentrations greater than 180 µg/ml usually develop severe CNS depression [28]. Taking VPA at higher doses (>400 mg/kg) is associated with serious consequences such as coma, cerebral oedema [29], metabolic acidosis, hyperammonemia, thrombocytopenia and leukopenia, and circulatory collapse [11, 30, 31]. The study by Spiller et al. [11] show that the concentration of VPA > 850 µg/ml was more likely to be associated with coma ($P < 0.005$). In a large multicentre review of 134 patients (80 with VPA levels in the toxic range), 71% of patients presented with lethargy, and 15% were in coma [8]. In our study, 15.39% of patients were in stage III coma (Matthew's scale). This study shows that the serum VPA concentration showed moderate positive correlations with Matthew's coma scale (*Spearman's rho* = 0.45, $P = 0.022$). This means that the higher the VPA concentration, the higher its score on Matthew's coma scale.

Other possible adverse effects of valproic acid on the nervous system include agitation, hallucinations, tremors, myoclonus and seizures [28].

In addition to generally known symptoms, valproic acid intoxication may also be associated with hypotension [32]. In this study, correlational analysis (*Pearson's r*) revealed a moderate negative correlation between VPA concentration and diastolic blood pressure ($r = -0.45$, $P = 0.022$). This negative correlation means that when the VPA level is higher, the diastolic blood pressure is lower.

Other clinical findings include respiratory depression and acute respiratory distress syndrome [33, 34]. In the study by Tank et al. [35], all patients with serum levels higher than 850 µg/ml were comatose, and 63% of these patients needed intubation.

In our study, out of 26 patients, only two experienced respiratory depression and required intubations. The first patient was a 49-year-old man, reportedly poisoned intentionally, admitted to Toxicology Department. His valproate sodium serum concentration was 224.8 µg/ml. The serum level of other drugs and ethanol were all negative. He had a history of psychiatric illness, including personality disorder and alcohol dependence syndrome. His vital signs were as follows: pulse rate 115 beats/min, blood pressure 155/100 mmHg, temperature 36.6°C and respiratory insufficiency. On the day of admission, the patient was unconscious, in the third stage coma by Matthew's scale, with features of overt respiratory failure. The patient was immediately intubated and connected to a respirator. After the first day the patient was extubated, had efficient breathing, but with persistent disturbances of consciousness, periodically extremely agitated and psychotic. Gradually, the patient's condition experienced an improvement. From the fifth day there was a logical, calm. When the serum levels returned to normal, the patient made a complete recovery. On the seventh day of treatment, after psychiatric review, the patient was discharged home in good condition. The second patient was a 24-year-old woman admitted to the Toxicology Department after attempting suicide by ingesting tablets of valproic acid. Her valproate sodium serum concentration was high and peaked at 315 µg/ml. The serum level of other drugs and ethanol were all negative. She had a history of psychiatric illness, including paranoid schizophrenia. The patient was confused, hallucinated

and developed deep coma. In addition, the physical examination revealed tachycardia 120 beats/min and normal blood pressure (110/70 mmHg). Her core body temperature was 36.8°C. In the early hours of observation, there were repeated spasms and respiratory insufficiency – the patient was intubated and connected to a respirator. Gradually, the patient's condition improved, and after 4 days of mechanical ventilation, the patient was extubated. In the fourth day the patient was in contact and began to walk in the fifth. Because of the high risk of recurrence of attempted suicide, the patient was urgently addressed without consent to the psychiatric ward for further treatment. At the time of discharge, the patient did not require hospitalization for toxicological reasons.

Haematological disturbances are rare, but there are potentially serious complication of chronic valproate therapy and overdose [11, 13]. Spiller et al. [11] demonstrated that thrombocytopaenia (<150 tys/ μ l), occurred with valproate concentrations >450 μ g/ml, but did not correlate it with dose ingested, whereas fatal leukopenia (WBC <1200 tys/ μ l) was observed in patients with VPA concentrations >1200 μ g/ml. Hypernatremia ($\text{Na}^+ > 145$ mmol/l) and hypocalcaemia were observed in patients with peak VPA concentrations >450 μ g/ml [13].

In our study, there were no reported haematological disturbances among the cases of VPA intoxications.

In our study, mean length of hospital stay for all patients was 4.69 days; in the study by Spiller et al. [11], it was 42 ± 33.1 hours. In this study, statistical analysis found the relationship between the serum concentration of VPA and the duration of stay in hospital ($P = 0.001$) and that the higher the drug concentration, the longer the length of stay in hospital for the patients.

In the case series by Spiller et al. [11], patients with peak valproic acid concentrations above 450 μ g/ml were more likely to develop significant clinical effects and have longer hospital stays ($P < 0.05$). Also, acute toxicity seems to be less severe in patients who are regularly taking valproate [36].

Few fatalities of valproic acid overdose are reported in the literature [11, 27, 35–41]. Deaths were associated with plasma concentrations ranging from 305.4 μ g/ml [37] to 1970 μ g/ml [27]. In our study, the highest related VPA level was 660 μ g/ml; however, the intoxication in this case was non-lethal.

6. Conclusions

1. Positive correlation of the serum VPA concentrations with diastolic blood pressure, poisoning severity score, Matthew's coma scale and length of stay in hospital has been found.
2. We failed to find any significant correlation between the VPA plasma level and the remaining parameters.

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