ORIGINAL ARTICLE

Favorable results after conservative management of 316 valproate intoxicated patients

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Background: Valproic acid (VPA) is an effective antiepileptic drug widely used worldwide. Despite several studies indicating the usefulness of intravenous L-carnitine in the treatment of VPA poisoning, this drug is not readily available in Iran. The aim of this study was to determine whether supportive care without antidote would result in acceptable outcomes in VPA poisoned patients. **Materials and Methods:** In an observational, retrospective, single-center case series, all patients >12-year-old with VPA overdose who had referred to a tertiary center between 2009 and 2013 were consecutively enrolled. Patients' demographic and presenting features, physical examinations, clinical management, laboratory data, and outcomes were recorded. **Results:** A total of 316 patients were enrolled with pure VPA toxicity. The most common presenting signs/symptoms were drowsiness, nausea and vomiting, vertigo, and headache. In the course of the disease, 14 patients (4.4%) were intubated and three (0.9%) required hemodialysis with mean dialysis sessions of two. Fourteen patients were admitted to Intensive Care Unit, and seizures occurred in five. The initial level of consciousness was lower in patients with poor outcome. The median ingested dose of VPA in patients who required dialysis was significantly higher (20 vs. 6 g; $P = 0.006$). Multivariate analyses revealed that coma on presentation was associated with a worse outcome ($P = 0.001$; odds ratio = 61.5, 95% CI = 5.8-646.7). **Conclusion:** Prognosis of VPA poisoned patients appears to be good even with supportive care. According to our study, older age, ingestion of higher amounts of VPA and lower PCO_2, HCO_3, base excess, and CPK levels prone the patients to more severe toxicities in univariate analysis, but the main poor prognostic factor is coma on presentation in multivariate analysis.

Key words: Anticonvulsants, antiepileptic drugs, overdose, suicide, poisoning, valproic acid

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INTRODUCTION

Valproic acid (VPA) or valproate is an effective antiepileptic drug widely used all over the world and approved for the treatment of both partial and generalized seizures.[1-4] It is also used to treat bipolar and schizoaffective disorders, social phobias, neuropathic pain, and for prophylaxis or treatment of migraine headaches.[2,3] The usual daily dose of 1-2 g in adults and 15-60 mg/kg in children is generally recommended. Serum valproate levels range from 50 μg/mL to 125 μg/mL, although a level more than 100 μg/mL in acute ingestion may be considered to be toxic and in levels higher than this cutoff point, hemodialysis may contribute to VPA elimination.[2,5,6]

When serum VPA level is over 100-150 μg/mL, protein sites are saturated leading to increased levels of the free drug.[2,3,5] VPA enhances gamma-aminobutyric acid synthesis and release in some specific areas of the brain that can control seizure onset and propagation.[2,6] Furthermore, VPA reduces the release

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of the epileptogenic acid and changes dopaminergic and serotoninergic neurotransmissions.[2,7] As VPA use has increased, reports on both accidental and intentional intoxications are increasing.[2,3,6]

VPA overdose usually causes mild and self-limited central nervous system depression. However, serious adverse effects and even death have been reported.[8,9] In addition to central nervous system depression, VPA toxicity may cause cerebral edema, hyperammonemia, and hepatotoxicity.[7,10]

Recent articles have shown that hepatotoxicity induced by VPA can be managed by L-carnitine. L-carnitine also increases the survival rate of these patients, especially in cases referred with coma, rising ammonia level, or VPA levels greater than 450 μg/mL.[3,11,12] However, some experts believe that L-carnitine has no specific therapeutic effect in acute overdose.[13] Despite several studies indicating the usefulness of intravenous L-carnitine in the treatment of VPA poisoning, this drug is not readily available in Iran. Many patients with severe acute VPA toxicity are supportively treated. The objective of this study was, therefore, to determine whether supportive care without antidote would result in acceptable outcome in acutely VPA poisoned patients and to find out the factors associated with poorer outcomes.

MATERIALS AND METHODS

After approval of the Ethical Committee of Human Research of the Clinical Research Development Center, all patients >12-year-old with acute VPA overdose who had been referred to Loghman-Hakim Hospital between 2009 and 2013 were consecutively enrolled. Those with multidrug ingestions were excluded [Figure 1]. In this observational, retrospective, single-center case series, patients were identified using the International Classification of Disease Codes (ICD10 codes version 2010). Those with code T42-6 (poisoning chapter; poisoning by antiepileptics, sedative-hypnotics, and antiparkinsonism drugs), X41 (accidental poisoning by and exposure to antiepileptics), X61 (intentional self-poisoning by and exposure to antiepileptics), and Y11 (antiepileptic poisoning, undetermined intent) were evaluated.

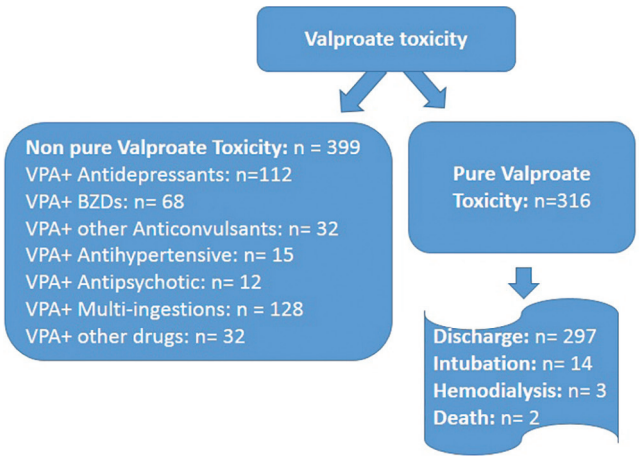

Figure 1: Selection and outcome of participants recruited in the study

Patients' demographic and presenting features, physical examinations, laboratory data, treatment modalities, and outcomes were recorded. On arrival, vital signs and laboratory findings, as well as those after initial stabilization (averagely 6 h after admission), were checked. The time elapsed between ingestion and presentation, as well as the ingested amount, was also recorded based on the patients' report or hospital admission. Severe toxicity was defined as the need for intubation and/or hemodialysis or death during hospitalization and those with poor prognosis were considered to have severe toxicity in the current study. Severity of poisoning was also determined based on the ingested dose as follow: Severe toxicity (>28 g or ~400 mg/kg), probable moderate toxicity (>14 g or ~200 mg/kg), probable mild toxicity (>1.8 g), and probable nontoxic ingestion (<1.8 g).[13,14] Patients with severe toxicity were compared to the remainder in order to determine the independent variables which would cause a worse outcome. The normal range of aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase (ALK/P), and carnitine phosphokinase were considered to be 5-40 IU/L, 7-56 IU/L, 44-147 IU/L, and 140-280 IU/L, respectively.[15]

All the patients had received standard care, including airway management, intravenous fluid resuscitation, gastrointestinal lavage, activated charcoal and sorbitol, and Intensive Care Unit (ICU) care/hemodialysis if indicated. As we did not access the serum level of VPA in all cases (just in 19.6%) and L-carnitine was also unavailable, we treated the patients conservatively and dialyzed them when they did not respond to conservative treatment. Activated charcoal was given within the 1st h postingestion, if the time of overdose was known. Intravenous L-carnitine was not prescribed to any patient because it is not available in Iran. This study was approved by the institutional review board.

Statistical analysis was performed by Statistical Package for Social Sciences (SPSS) version 18.0 (SPSS Inc., Chicago, IL, USA) using Shapiro-Wilk, Chi-square and Fisher's exact tests, Wilcoxon signed-rank test, Mann-Whitney U-test, Kruskal-Wallis H-test, and binomial logistic regression test. Statistical significance was set at $P < 0.05$.

RESULTS

Of a total of 715 patients, 316 were enrolled as pure VPA toxicity [Figure 1] with a female to male ratio of 2.55. The

median (interquartile range [IQR]) age was 23 (18, 30 [range; 10-66 years]). The median (IQR) ingested dose of VPA was 600 (400, 1000 mg [range; 400-4000 mg]). However, the exact intake dose of 44 patients (13.9%) was unknown. In 286 patients (90.5%), the exact time of ingestion was reported by the patients themselves or their accompanying relatives. Median (IQR) time elapsed between drug ingestion and hospital presentation was 4 (2, 7 h [range; 1-72 h]). All the patients had deliberately poisoned themselves as confirmed by psychiatric assessments. Gastric lavage and/or activated charcoal administration were performed in 178 (56.3%) patients. The most common underlying diseases were epilepsy (56 patients), psychosis (32 patients), depression (24 patients), and migraine headaches (13 patients). However, 166 (52.5%) intoxicated cases did not have any underlying diseases. The most common presenting signs/symptoms were drowsiness (70 patients, 22.2%), nausea and vomiting (60 patients, 19.1%), vertigo (43 patients, 13.6%), and headache (34 patients, 10.8%).

In 223 cases (70.6%), electrocardiograms (ECGs) were normal on presentation. The most common ECG abnormalities included sinus tachycardia (46 patients, 14.6%) followed by sinus bradycardia (16 patients, 5.1%). In the course of the disease, 14 patients (4.4%) were intubated and three (0.9%) required hemodialysis with the mean dialysis sessions of two. ICU admission was needed in 14 patients (4.4%). Mean ICU stay was 80 ± 57 h while the median (IQR) hospital stay was 15 (12, 24) h. Seizures occurred in five patients (1.4 %) during hospitalization, none of whom had a history of epilepsy. The average ingested dose of VPA was 6.5 ± 6.3 g (range, 2-16 g). There was no association between the occurrence of seizures and poor outcomes ($P = 0.204$, Fisher's exact test).

The initial level of consciousness was lower in patients with poor outcomes. On the other hand, only 0.7% of the patients who discharged without any complications had been admitted to an emergency department in coma. Table 1 shows the comparison between the patients with fair and poor outcomes. A total of 7.6% and 1.4% of the patients had abnormal AST and ALT on admission with no significant association between these tests and patients' outcome. ALK/P was abnormal in 56% of the patients who had the documented levels of this test in their files and was not significantly different between those with fair and poor outcomes. None of the patients with nontoxic ingestions (<1.8 g) had abnormal AST, ALT, or ALK/P. Table 2 shows that although there was a significant correlation between probable mild/moderate/severe toxicity based on the ingested dose and poor outcome ($P < 0.005$), such a significant relation was not found between VPA level and outcome ($P = 0.404$, Kruskal-Wallis test). Table 3 shows the characteristics of 14 patients with poor outcomes.

The median ingested dose of VPA in patients who required dialysis was significantly higher (20 vs. 6 g; $P = 0.006$). However, median VPA serum concentration failed to show such significant difference between the two groups (150 vs.

Table 1: Comparison between the patients with good and poor outcome

Variable	Total (*n* = 316)	Good outcome (*n* = 302)	Poor outcome (*n* = 14)	*P* value (applied statistical test)
Age	23 (18, 30)	22.5 (18, 29)	31.5 (26, 47.5)	0.003 (MWU)
Gender				
Female	227 (71.8)	219 (72.5)	8 (57.1)	NS (Pearson χ^2)
Male	89 (28.2)	83 (27.5)	6 (42.9)	
Ingested dose (g)	6 (4, 10)	6 (4, 10)	17 (6, 20)	0.002 (MWU)
Time elapsed (h)	4 (2, 7)	4 (2, 7)	5 (3, 6.5)	NS (MWU)
Serum concentration (μg/mL)	118 (37, 188)	117 (31, 186)	129 (47, 226)	NS (MWU)
Coma on presentation				
Yes	9 (2.8)	2 (0.7)	7 (77.8)	0.0005 (Fisher exact test)
No	297 (97.2)	300 (99.3)	2 (22.2)	
SBP (mmHg)	110 (110, 120)	110 (110, 120)	120 (100, 122)	NS (MWU)
DBP (mmHg)	70 (65, 80)	70 (65, 80)	70 (60, 80)	NS (MWU)
RR (per min)	16 (14, 18)	16 (14, 18)	16 (13, 18)	NS (MWU)
HR (per min)	82 (80, 90)	82 (80, 90)	84 (78, 100)	NS (MWU)
Axillary T (°C)	37 (37, 37)	37 (37, 37)	37 (37, 37)	NS (MWU)
pH	7.39 (7.35, 7.42)	7.39 (7.35, 7.41)	7.42 (7.34, 7.45)	NS (MWU)
PCO_2 (mEq/L)	41.1 (36.2, 45.9)	41.2 (36.7, 46.7)	34.6 (29.5, 44.5)	0.045 (MWU)
HCO_3 (mEq/L)	24.2 (21.7, 27.3)	24.9 (22.1, 27.3)	21 (19.4, 24.1)	0.01 (MWU)
BE (mEq/L)	0 (−3, 1.9)	0.3 (−2.8, 2.3)	−2.5 (−4.3, −1.2)	0.03 (MWU)
CPK (IU/L)	99 (65, 155)	100 (72, 196)	60 (44, 127)	0.038 (MWU)
Hospital stay (h)	15 (12, 24)	15 (11, 24)	104 (52, 127)	0.0005(MWU)

Data were presented as median value (inter quartile range) or *n* (%). MWU = Mann-Whitney U-test; SBP = Systolic blood pressure; DBP = Diastolic blood pressure; RR = Respiration rate; HR = Heart rate; CPK = Creatine phosphokinase; NS = Not significant

117 μg/mL; $P = 0.182$). Ammonia level was not measured in any of the patients who underwent dialysis.

Evaluation of the platelets using Wilcoxon signed-rank test showed no evidence to approve thrombocytopenia as an indicator of severe valproate toxicity. On the other hand, pH, PCO_2, HCO_3, and liver function tests (AST, ALT, and ALK/P) evaluated in the patients with poor outcomes showed no statistically significant difference between these parameters on admission and before death or discharge (Wilcoxon signed-rank test). Multivariate analysis revealed that coma on presentation was associated with the worst outcome ($P = 0.001$; odds ratio = 61.5; 95% CI = 5.8-646.7).

DISCUSSION

There is no controlled, randomized trial that delineate the therapeutic and prophylactic roles of L-carnitine and the optimal regimen of its administration in VPA toxicity. To compare treatment with or without L-carnitine, the only way is to review those studies that used this antidote and compare final outcomes with the ones which did not use it.

Valproate is widely prescribed for the treatment of epilepsy with few side effects although its toxicity has been steadily increasing in frequency worldwide.[1,3,6,16-19] Our previous data from 2003 showed that in 6 months only 51 pure VPA toxicity cases had been admitted to our center.[20] In the current study, 316 cases were hospitalized in 36 months which again confirms this claim. The frequency of anticonvulsant and benzodiazepine toxicities were almost constant between 2006 and 2011 (F [5-2.70] = 0.22, $P = 0.93$).[21]

VPA is generally well tolerated, but rare serious adverse events may occur in some patients receiving it, including hemorrhagic pancreatitis, bone marrow suppression, hepatotoxicity, and VPA-induced encephalopathy.[2] Our data showed no sign of bone marrow suppression including thrombocytopenia in our patients during hospitalization. The same results were found by Isbister *et al*.[16] On the other hand, while liver function tests did not significantly affect the patients' outcome, ALK/P was interestingly high in the majority of the patients with ingestion of toxic doses (56%).

Initial vital signs were shown to have no significant effect on the final outcome of the patients. In univariate analysis, the only independent factors which correlated with poorer outcome were older age, higher ingested doses, coma on presentation, lower PCO_2, HCO_3, base excess, and CPK, and not surprisingly, prolonged hospital stay [Table 1]. Unlike Spiller *et al*. and Thanacoody studies, we could not find any association between serum VPA level and outcome.[8,22] This may be due to different presentation and sampling times.

Although it is claimed that the massive overdoses (>400 mg/kg) of valproate are potentially life-threatening and can lead to poor outcomes, we had some patients presenting with mild overdoses who developed hepatotoxicity, loss of consciousness, and even death. Overall, the outcome is good in VPA toxicity and the number of patients with

Table 2: Correlation of ingested dose and poor outcome in 272 patients with known ingested dose

Characteristics	Potentiality of toxicity				
	Nontoxic	Mild	Moderate	Severe	Total
Good outcome number (%)	15 (100)	224 (98.2)	21 (80.8)	2 (66.7)	262 (96.3)
Poor outcome number (%)	0	4 (1.8)	5 (19.2)	1 (33.3)	10 (3.7)
Total number (%)	15 (100)	228 (100)	26 (100)	3 (100)	272 (100)

Table 3: On-arrival characteristics of 14 intubated patients

n	Age (years) and gender	Elapsed hours (ingestion-admission)	Dose (g)	Serum concentration (μg/mL)	Coma on presentation	Acidosis	ECG findings	Abnormal LFT	Dialysis/ numbers	Hospital stay (h)	Death
1	37 female	–	20	120	No	No	Normal	Yes	Yes/3	264	No
2	29 female	5	–	–	Yes	No	Tachycardia	No	No	120	No
3	35 male	–	30	550	Yes	Yes	Normal	Yes	Yes/1	80	Yes
4	20 female	–	20	54	Yes	No	Normal	No	No	120	No
5	50 male	7	60	129	No	No	Tachycardia	Yes	No	110	Yes
6	33 male	3	–	–	No	No	Normal	Yes	No	30	No
7	28 female	1	16	150	No	No	Normal	Yes	Yes/2	210	No
8	53 female	4	4	–	No	No	Prolonged QT	No	No	40	No
9	20 female	–	6	–	Yes	No	Tachycardia	Yes	No	60	No
10	16 female	3	20	303	Yes	Yes	Normal	Yes	No	56	No
11	28 male	19	18	22.5	Yes	Yes	Normal	Yes	No	148	No
12	49 male	–	–	41.8	Yes	No	Normal	Yes	No	20	No
13	47 female	6	10	229	No	No	Tachycardia	No	No	98	No
14	3 male	5	20	120	No	No	Normal	No	No	120	No

Acidosis and LFT were evaluated during hospitalization. LFT = Liver function tests; ECG = Electrocardiogram

poor outcome is quite few (4.4%) and death is uncommon (0.6%). Most studies on VPA toxicity are case reports. Isbister *et al*. reported a fatal case of VPA toxicity among 79 cases; however, it was a mixed ingestion of drugs.[16] We had no deaths in our previous study in 51 pure VPA toxicity cases.[20]

Published evidence on the efficacy and safety of L-carnitine for acute VPA overdose is not enough.[1,2] Perrott *et al*. stated that it was reasonable to consider L-carnitine for patients with acute VPA overdose and decreased level of consciousness.[23] Mock and Schwetschenau concluded that oral levocarnitine was safe and effective in VPA-induced encephalopathy.[24] L-carnitine has also been used with questionable benefit in the setting of acute VPA-induced hepatitis.[25] In a recent study, Lheureux and Hantson mentioned that early intravenous L-carnitine improved survival in severe VPA-induced hepatotoxicity.[1] In our study, intravenous L-carnitine was not used and conservative management had arguably resulted in the similar results. We are not yet able to decline or confirm the usefulness of L-carnitine in acute VPA toxicity although it seems a safe antidote.[11,13,18,23,24]

In terms of hemodialysis, we were not dependent on ammonia level.[22] Hemodialysis was done in three patients unresponsive to supportive care and the progress of the loss of consciousness and probable encephalopathy. None of them had a serum VPA more than 850 μg/mL which was considered for HD by previous studies.[16,22] One of the dead cases was dialyzed one time and we think that early HD might have saved his life. L-carnitine may be used in this situation as well, but the formation of ammonia is higher due to higher VPA concentrations. Some authors suggest measuring ammonia during VPA toxicity treatment.[25]

STRENGTH AND LIMITATIONS

To the best of our knowledge, this is the largest single-center study on pure VPA toxicity. The retrospective nature of this study along with missing data, lab tests, valproate level (measured in 62 cases), and ammonia level (measured in only three cases) were definitely the main limitations of this study. The valproate level was not measured on arrival in all the cases; thus there was no correlation between ingested dose and valproate level. Inability to follow all outpatients in order to measure the probable late consequences of VPA toxicity is another potential limitation.

CONCLUSIONS

The prognosis of patients with acute VPA toxicity appears to be good even with supportive care. According to our study, the main poor prognostic factor is coma in the multivariate analysis which may be seen after the ingestion of doses as low as 6 g. In univariate analysis, older age and ingestion of higher amounts of VPA prone the patients to more severe toxicities. Lower PCO_2, HCO_3, BE, and CPK are other variables which can be used to predict the outcome of toxicity.

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Conflicts of interest

There are no conflicts of interest.

AUTHOR'S CONTRIBUTION

SS and HA designed the study. NGh and MR acquiesced the data. NZ, ZV and HHM drafted the article, HHM analysed and interpreted the data. All authors made substantial contribution for final approval of the current article.

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