All guns blazing: management and survival of massive valproic acid overdose – case report and literature review

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Abstract: A 51-year-old woman, who intentionally ingested a massive dose of ~60 g of valproic acid which she was using as a mood stabilizer for bipolar affective disorder, presented within 30 minutes of ingestion to the emergency department. The patient was asymptomatic and was immediately started on decontamination therapy with activated charcoal (AC). Drug serum levels, liver functions, and ammonia levels were tested and followed up during treatment. Due to the massive ingestion and continuous rise in serum drug levels, the patient received regular multiple doses of AC, as well as L-carnitine for liver protection. The patient was started on extracorporeal therapy in the form of renal replacement therapy in the intensive care unit (ICU), followed by intermittent hemodialysis. Drug serum levels dropped significantly. Ammonia levels showed improvement with treatment. The patient was discharged from the ICU after 14 days of treatment. She was stable and in good condition with no residual hepatic or central nervous system (CNS) manifestations.

Keywords: valproic acid, multiple dose activated charcoal, L-carnitine, hemodialysis

Introduction
Valproic acid (VPA) has been primarily used as an anticonvulsant since 1967, and later, Lambert et al reported an additional antimanic property. Further studies in Germany and the United States demonstrated its efficacy, and by 1995, the US Food and Drug Administration approved the use of VPA for such indications. VPA works by increasing the availability of gamma-aminobutyric acid (GABA) in the brain. It is metabolized primarily in the liver and has an average half-life of 9–19 hours in a healthy adult. Time to peak concentration differs according to the product (regular, delayed, and extended-released) from 2 to 17 hours and it is mainly excreted in urine. Trough levels are used to assess the therapeutic effect of the medication. Therapeutic dosages between 50–100 µg/mL and 50–125 µg/mL are adequate for epilepsy and mania, respectively. Levels >450 mg/L have been found to cause severe life-threatening clinical manifestations such as severe central nervous system (CNS) depression, hepatotoxicity, hyperammonemia, and cerebral edema which can be clinically apparent as early as 12 hours following ingestion.

Case presentation
A 51-year-old woman known to have bipolar affective disorder presented to the emergency department (ED) having overdosed on 120 tablets of VPA (Depakene®) 30 minutes prior to her arrival. Each tablet was of 500 mg strength; a total of 60 g was ingested. She had a history of attempting suicide and had been treated with VPA
as a mood stabilizer. The patient had no specific complaints. Initial patient vital signs were as follows: temperature, 37°C; blood pressure, 147/75 mmHg; heart rate, 102 bpm; oxygen saturation, 99% on room air; and respiratory rate, 20 breaths per minute. On physical examination, the patient was conscious, alert, and oriented to time, place, and person. The rest of the physical examination was unremarkable. An electrocardiogram was done and showed sinus tachycardia. Blood was drawn and sent for testing for VPA levels at 0 and 4-hour intervals. Complete blood count, renal and liver functions, ammonia levels, and venous blood gas were also done, and the results are shown in Table 1.

The patient was managed initially in the ED by 50 g of activated charcoal (AC). The lab reported that her VPA level was 379.6 µg/mL, and additional multiple doses of AC were started at a dose of 0.5 g/kg every 4 hours. Also, a loading dose of L-carnitine was administered (100 mg/kg intravenously over 3 minutes). This was followed by maintenance doses of L-carnitine at 15 mg/kg every 4 hours over 10–30 minutes to be continued during admission. The patient was referred to the intensive care unit (ICU) team for further management and admission. VPA levels were repeatedly tested every 4 hours. At 4 hours following presentation, VPA levels were measured to be 764 µg/mL and were on the rise.

The patient developed seizures and a depressed level of consciousness 8 hours following presentation and was then intubated. Twelve hours after presentation VPA level reported from the laboratory was 905 µg/mL. At the time, continuous renal replacement therapy (CRRT) was planned, which was started almost 24 hours after presentation. Eight hours following CRRT, VPA levels were tested and showed a significant drop to 417 µg/mL. At this point, hemodialysis (HD) was initiated for 8 hours, and the level dropped further to 94 µg/mL. A computed tomography (CT) scan of the brain was done, and the results were unremarkable. Ammonia levels were initially elevated, reaching up to 393 mmol/L by the second day, but improved with management.

| Table 1 Laboratory tests day by day during the hospital admission |
|-------------------------|-------------------------|-------------------------|
| **Day of admission**    | **Renal function test** (RFT) | **Liver function test** (LFT) | **Ammonia level NL (11–32)** |
| Day 1                   | BUN = 4 (mg/dL)          | T Bili = 0.2 (mg/dL)     | 58 (mmol/L)               |
|                        | Creat = 0.6 (mg/dL)      | D Bili = 0.1 (mg/dL)     |                           |
|                        | Na = 142 (mEq/L)         | Albumin = 3.1 (g/dL)    |                           |
|                        | K = 4.6 (mEq/L)          | SGOT = 13 (U/L)         |                           |
|                        |                          | SGPT = 19 (U/L)         |                           |
|                        |                          | GGTP = 20 (U/L)         |                           |
| Day 2                   | BUN = 4 (mg/dL)          | T Bili = 0.2 (mg/dL)     | 393 (mmol/L)              |
|                        | Creat = 0.9 (mg/dL)      | D Bili = 0.1 (mg/dL)     |                           |
|                        | Na = 148 (mEq/L)         | Albumin = 3.2 (g/dL)    |                           |
|                        | K = 3.1 (mEq/L)          | SGOT = 17 (U/L)         |                           |
|                        |                          | SGPT = 17 (U/L)         |                           |
|                        |                          | GGTP = 18 (U/L)         |                           |
| Day 3                   | BUN = 6 (mg/dL)          | T Bili = 0.3 (mg/dL)     | Not measured              |
|                        | Creat = 0.7 (mg/dL)      | D Bili = 0.1 (mg/dL)     |                           |
|                        | Na = 147 (mEq/L)         | Albumin = 2.9 (g/dL)    |                           |
|                        | K = 2.9 (mEq/L)          | SGOT = 19 (U/L)         |                           |
|                        |                          | SGPT = 16 (U/L)         |                           |
|                        |                          | GGTP = 20 (U/L)         |                           |
| Day 4                   | BUN = 10 (mg/dL)         | T Bili = 0.3 (mg/dL)     | 70 (mmol/L)               |
|                        | Creat = 1.0 (mg/dL)      | D Bili = 0.1 (mg/dL)     |                           |
|                        | Na = 141 (mEq/L)         | Albumin = 2.4 (g/dL)    |                           |
|                        | K = 3.7 (mEq/L)          | SGOT = 15 (U/L)         |                           |
|                        |                          | SGPT = 14 (U/L)         |                           |
|                        |                          | GGTP = 16 (U/L)         |                           |
| Day 5                   | BUN = 10 (mg/dL)         | T Bili = 0.4 (mg/dL)     | 30 (mmol/L)               |
|                        | Creat = 0.6 (mg/dL)      | D Bili = 0.1 (mg/dL)     |                           |
|                        | Na = 139 (mEq/L)         | Albumin = 2.0 (g/dL)    |                           |
|                        | K = 2.6 (mEq/L)          | SGOT = 12 (U/L)         |                           |
|                        |                          | SGPT=15 (U/L)           |                           |
|                        |                          | GGTP = 20 (U/L)         |                           |

(Continued)
### Table 1 (Continued)

| Day of admission | Renal function test* (RFT) | Liver function test* (LFT) | Ammonia level NL (11–32) |
|------------------|---------------------------|---------------------------|--------------------------|
| Day 6            | BUN = 6.0 (mg/dL)         | T Bili = 0.8 (mg/dL)      | 50 (mmol/L)              |
|                  | Creat = 0.6 (mg/dL)       | D Bili = 0.3 (mg/dL)      |                          |
|                  | Na = 140 (mEq/L)          | Albumin = 1.9 (g/dL)     |                          |
|                  | K = 2.8 (mEq/L)           | SGOT = 21 (U/L)          |                          |
|                  |                            | SGPT = 18 (U/L)          |                          |
|                  |                            | GGTP = 39 (U/L)          |                          |
| Day 7            | BUN = 13 (mg/dL)          | T Bili = 1.1 (mg/dL)      | 61 (mmol/L)              |
|                  | Creat = 0.8 (mg/dL)       | D Bili = 0.6 (mg/dL)      |                          |
|                  | Na = 142 (mEq/L)          | Albumin = 2.4 (g/dL)     |                          |
|                  | K = 3.5 (mEq/L)           | SGOT = 18 (U/L)          |                          |
|                  |                            | SGPT = 22 (U/L)          |                          |
|                  |                            | GGTP = 43 (U/L)          |                          |
| Day 8            | BUN = 9 (mg/dL)           | T Bili = 1.6 (mg/dL)      | 40 (mmol/L)              |
|                  | Creat = 0.6 (mg/dL)       | D Bili = 1.0 (mg/dL)      |                          |
|                  | Na = 144 (mEq/L)          | Albumin = 2.4 (g/dL)     |                          |
|                  | K = 3.1 (mEq/L)           | SGOT = 25 (U/L)          |                          |
|                  |                            | SGPT = 27 (U/L)          |                          |
|                  |                            | GGTP = 45 (U/L)          |                          |
| Day 9            | BUN = 10 (mg/dL)          | T Bili = 1.3 (mg/dL)      | 41 (mmol/L)              |
|                  | Creat = 0.5 (mg/dL)       | D Bili = 0.8 (mg/dL)      |                          |
|                  | Na = 146 (mEq/L)          | Albumin = 2.2 (g/dL)     |                          |
|                  | K = 3.8 (mEq/L)           | SGOT = 58 (U/L)          |                          |
|                  |                            | SGPT = 59 (U/L)          |                          |
|                  |                            | GGTP = 37 (U/L)          |                          |
| Day 10           | BUN = 9 (mg/dL)           | T Bili = 1.2 (mg/dL)      | 56 (mmol/L)              |
|                  | Creat = (mg/dL)           | D Bili = 0.7 (mg/dL)      |                          |
|                  | Na = (mEq/L)              | Albumin = 1.8 (g/dL)     |                          |
|                  | K = (mEq/L)               | SGOT = 75 (U/L)          |                          |
|                  |                            | SGPT = 70 (U/L)          |                          |
|                  |                            | GGTP = 33 (U/L)          |                          |
| Day 11           | BUN = 9 (mg/dL)           | T Bili = 2.1 (mg/dL)      | 24 (mmol/L)              |
|                  | Creat = 0.4 (mg/dL)       | D Bili = 1.1 (mg/dL)      |                          |
|                  | Na = 141 (mEq/L)          | Albumin = 2.7 (g/dL)     |                          |
|                  | K = 4.4 (mEq/L)           | SGOT = 58 (U/L)          |                          |
|                  |                            | SGPT = 72 (U/L)          |                          |
|                  |                            | GGTP = 70 (U/L)          |                          |
| Day 12           | BUN = 16 (mg/dL)          | T Bili = 1.1 (mg/dL)      | 23 (mmol/L)              |
|                  | Creat = 0.4 (mg/dL)       | D Bili = 0.5 (mg/dL)      |                          |
|                  | Na = 142 (mEq/L)          | Albumin = 3 (g/dL)       |                          |
|                  | K = 4.7 (mEq/L)           | SGOT = 25 (U/L)          |                          |
|                  |                            | SGPT = 48 (U/L)          |                          |
|                  |                            | GGTP = 66 (U/L)          |                          |
| Day 13           | BUN = 16 (mg/dL)          | T Bili = 1.0 (mg/dL)      | Not measured             |
|                  | Creat = 0.3 (mg/dL)       | D Bili = 0.5 (mg/dL)      |                          |
|                  | Na = 140 (mEq/L)          | Albumin = 3.3 (g/dL)     |                          |
|                  | K = 4.4 (mEq/L)           | SGOT = 28 (U/L)          |                          |
|                  |                            | SGPT = 51 (U/L)          |                          |
|                  |                            | GGTP = 75 (U/L)          |                          |
| Day 14           | BUN = 19 (mg/dL)          | T Bili = 0.9 (mg/dL)      | Not measured             |
|                  | Creat = 0.5 (mg/dL)       | D Bili = 0.4 (mg/dL)      |                          |
|                  | Na = 143 (mEq/L)          | Albumin = 3.0 (g/dL)     |                          |
|                  | K = 4 (mEq/L)             | SGOT = 32 (U/L)          |                          |
|                  |                            | SGPT = 50 (U/L)          |                          |
|                  |                            | GGTP = 88 (U/L)          |                          |

**Notes:** The normal values for RFT: BUN = 7–18 (mg/dL), Creat = 0.5–1.0 (mg/dL), K = 3.5–5.1 (mEq/L), and Na = 136–145 (mEq/L), and normal values for LFT: T Bili = 0.1–1.0 (mg/dL), SGPT = 14–63 (U/L), GGTP = 5–55 (U/L), SGOT = 15–37 (U/L), D Bili = 0.0–0.4 (mg/dL), albumin = 3.4–5.0 (g/dL). Values in bold are abnormal laboratory blood test levels.

**Abbreviations:** Creat, creatinine; LFT, liver function test; NL, normal level; RFT, renal function test.
further VPA level drops and clinical improvement, sedation was stopped, and the patient was successfully extubated on the 12th day of admission. By day 14, she was transferred to the psychiatry ward in good and stable condition for further management of her primary illness. Figure 1 shows the serial level for valproic acid and Table 1 shows laboratory test results over days of treatment.

The patient’s stay in the psychiatry unit was uneventful; during the stay she was started on olanzapine, lorazepam, and escitalopram. The patient was discharged after 2 weeks and a follow-up appointment in psychiatry outpatient clinic was scheduled.

**Ethical statement**
The patient provided written informed consent for the case details to be published.

**Discussion**
VPA is metabolized in the liver. In the case of overdose, it binds to carnitine within the hepatocytes to form the VPA–carnitine complex leading to carnitine deficiency. This impairs fatty acid oxidation causing steatosis and liver failure. Furthermore, VPA–carnitine oxidation in the mitochondria produces 2-propyl-4-pentenoic acid (4-EN-VPA), which interferes with the urea cycle and causes hyperammonemia.6,7

We report a case of a middle-aged woman who intentionally ingested a massive dose of ~60 g of VPA, which she had been using as a mood stabilizer for the preceding year to treat her bipolar affective disorder. Her course of treatment required ICU admission and intubation to protect her airway due to CNS depression which is a known complication of high doses of such medication. Her care was managed using the best available information on drug toxicity, multi doses of AC, L-carnitine, HD, intensive ventilation and other supportive and ICU bundle measures. She improved after 12 days and was extubated. Two days later she was discharged from the ICU.

Management of VPA toxicity varies due to the lack of well-designed controlled studies supporting any of the interventions used currently such as AC, L-carnitine, and HD. The only available guidelines for VPA poisoning management were published in 2008 and were primarily based on a review of the American Association of Poison Control Center’s data of over 9,000 ingestions. All C and D recommendations were the highest grade of evidence of these guidelines, which means recommendations are extracted from case series, single case reports, or poor-quality cohort and case–control studies for the C recommendations, and expert opinion without explicit critical appraisal or based on physiology or bench research for the D recommendations.7 Table 2 shows

![Figure 1 Valproic acid level in association with intervention.](image)

**Abbreviations:** AC, activated charcoal; CRRT, continuous renal replacement therapy; HD, hemodialysis.
some of these reported cases and studies in the literature with different management approaches and outcomes.

In our case, we used the three main interventions (multidose AC, L-carnitine, and HD) that have been reported in the literature. In regard to AC, one prospective observational study investigated its efficacy on VPA absorption in volunteers. The results showed a significant decrease in the peak serum level by 65%; \( P < 0.01 \) when 50 g of AC was used within 5 minutes of ingestion. Compared to our case, AC was started within the first 30 minutes then multidoses of AC were continued; however, the levels continued to get higher, but we were unsure whether an increased level would have been reported higher if intervention was not started.8

The hypothesis behind the use of L-carnitine, our second intervention, is that VPA toxicity causes an inhibiting effect of carnitine synthesis during VPA toxicity by decreasing the concentration of \( \alpha \)-ketoglutarate. Because of this, adding L-carnitine may increase the \( \beta \)-oxidation of VPA, thereby decreasing the production of toxic metabolites that may cause liver toxicity. In our scenario, treatment with L-carnitine started within the first 6 hours of toxicity, and we are of the opinion that despite a very high level of VPA and an increased level of ammonia, the liver function was treating a benign course, possibly due to the early use of L-carnitine.

The last option for therapy used in managing our patient was HD. The role of HD in some overdoses is clearly studied, with proven efficacy. For VPA toxicity, the role of HD is not well defined. In our case, HD was started after almost 24 hours due to the continuous rise in the drug serum levels and worsening of our patient’s CNS function. Eight hours after starting HD in the form of CRRT, VPA levels dropped significantly to 417 µg/mL, and then treatment switched to intermittent HD and the levels dropped further to 94 µg/mL. We strongly believe that HD was the most effective intervention in the management of this patient and that it led to the rapid drop in her drug serum level and improvement of her clinical condition. For a drug to be dialyzable, it should be less protein bound. VPA at therapeutic levels is found to be ~90% plasma protein binding, but in the case of overdose or higher serum levels, the protein-binding property decreases and more of the drug is left free in the serum. In levels of >500 mg/L, possibly <10% is protein bound.9

Intermittent HD is the preferred modality of renal replacement therapy in VPA poisoning. If HD is not available, then intermittent hemoperfusion or CRRT is an acceptable alternative. The end point of HD includes clinical stabilization and VPA levels < 100 mg/L.9 As in many other cases of intoxication, it is important to monitor VPA levels after the cessation of HD, since redistribution of the medication can cause reemergence of toxicity.

**Conclusion**

We report a fortunate outcome for a case of a life-threatening intentional overdose of VPA. The patient showed progressive deterioration of her central neurological functions and was managed by a combination of supportive measures of airway protection, mechanical ventilation plus early decontamination with AC, L-carnitine therapy for her liver toxicity protection, and finally, extracorporeal therapy in the form of CRRT and intermittent HD. We believe that the early aggressive combination of these interventions had a great impact and led to a benign course for this patient during her ICU and hospital stay with complete recovery with no adverse sequelae.

**Disclosure**

The authors report no conflicts of interest in this work.

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