The Consequences of Valproate Overdose

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CASE

A 43-year-old man with epilepsy who had been treated with valproic acid (Depakote®) (VPA)2 for 13 years and had a history of multiple suicide attempts and alcohol dependence presented after ingesting an overdose of VPA and ibuprofen. The patient was not on any other prescribed medications. At presentation, the patient exhibited the following: Glasgow Coma Score (GCS), 3/15 (3 being the worst, indicating full coma, and 15 being a normal mental state); heart rate, 96 beats/min; blood pressure, 121/79 mmHg; temperature, 36.5 °C; oxygen saturation, 97%.

The patient’s plasma VPA concentration 3 h after admission was 1000 µmol/L (therapeutic interval, 50–100 µmol/L) and increased to 1400 µmol/L 14 h after admission. The amount of valproic acid ingested could not be determined from the case history, and it was not possible to accurately calculate the amount ingested because the absorption, the volume of distribution, and the elimination constant of VPA can be altered after an overdose. Paracetamol (acetaminophen), salicylate, and ethanol concentrations in blood were below their respective detection limits. The results of a computed tomography scan of the brain and an electroencephalography evaluation were normal. The amount of ibuprofen taken was unknown, and the plasma concentration was not measured.

Of particular note in the results of the admission biochemistry blood tests (Table 1) were an increased plasma osmolality (osmolal gap, <10 mmol/L on admission), an increased anion gap (AG), a low glucose concentration, and increased alanine aminotransferase activity. Blood gas results were unremarkable apart from an increased O2 partial pressure (P O2) 32.3 kPa (fraction of inspired oxygen, 50%) and an increased lactate concentration of 4.9 mmol/L. Additional blood investigations 2 h after admission showed severe hyperammonemia (ammonia, >286 µmol/L; upper reference limit, 55 µmol/L), hypernatremia, an increased plasma osmolality, and an increased AG (Table 1). The results of a urine screen for drugs of abuse were negative. The patient developed a profound respiratory alkalosis 6–10 h after admission secondary to the hyperammonemia.

Initial treatment involved standard intravenous rehydration with Hartmann solution (131 mmol/L Na+, 5 mmol/L K+, 2 mmol/L Ca2+, 29 mmol/L lactate, and 111 mmol/L Cl−), naloxone because of his reduced consciousness, and N-acetylcysteine as a precautionary measure. The patient was then transferred to the intensive care unit, where he received a 6-g infusion of L-carnitine over 16 h (approximately 100 mg/kg), with the aim of normalizing his ammonia concentration (as recommended by the UK National Poisons Unit). Hemodialysis was performed to aid in VPA removal. The initial attempt was unsuccessful because the patient had poor venous access. At 36 h after admission, hemodialysis removed 0.5 L of fluid, and an additional hemodialysis session (63 h after admission) removed another 0.5 L of fluid. The patient’s recovery was slow, with a GCS of 6/15 by day 4 and further improvement to 12/15 by day 6. He received 7 days of total parenteral nutrition. During this initial period, he developed thrombocytopenia and mild hypocalcemia (Table 1). The hypocalcemia was treated with Calci chew D3 Forte (2 tablets daily; Shire Pharmaceuticals).

A number of pseudoseizures were documented over several weeks. VPA therapy was briefly reintroduced 7 days after admission when plasma concentrations were below the therapeutic interval, but it was discontinued 17 days later because of the recurrence of thrombocytopenia. Lamotrigine was then introduced at a starting dosage of 25 mg once daily. The dosage was

QUESTIONS TO CONSIDER

1. What was the cause of the increased AG observed in this patient?
2. Why do individuals taking VPA develop increased ammonia concentrations?
3. What was the cause of hypernatremia in this patient?
4. Is it beneficial to measure free VPA or VPA metabolite concentrations in overdose cases?
Table 1. Routine biochemistry results for the patient during hospitalization.\(^a\)

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Reference interval</th>
<th>Admit</th>
<th>2 h</th>
<th>24 h</th>
<th>48 h</th>
<th>72 h</th>
<th>96 h</th>
<th>120 h</th>
<th>1 week</th>
<th>2 weeks</th>
<th>3 weeks</th>
<th>4 weeks</th>
</tr>
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<tbody>
<tr>
<td>Na(^+), mmol/L</td>
<td>135–145</td>
<td>145</td>
<td>153</td>
<td>150</td>
<td>136</td>
<td>140</td>
<td>137</td>
<td>134</td>
<td>134</td>
<td>136</td>
<td>138</td>
<td>137</td>
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<tr>
<td>HCO(_3^-), mmol/L</td>
<td>22–33</td>
<td>26</td>
<td>22</td>
<td>21</td>
<td>18</td>
<td>18</td>
<td>17</td>
<td>18</td>
<td>20</td>
<td>24</td>
<td>28</td>
<td>26</td>
</tr>
<tr>
<td>AG, mmol/L</td>
<td>6–16</td>
<td>22</td>
<td>30</td>
<td>27</td>
<td>20</td>
<td>15</td>
<td>12</td>
<td>12</td>
<td>14</td>
<td>12</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>pH</td>
<td>7.38–7.44</td>
<td>7.42</td>
<td>7.40</td>
<td>7.65</td>
<td>7.56</td>
<td>7.49</td>
<td>7.48</td>
<td>7.48</td>
<td>—</td>
<td>7.48</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>VPA, mg/L</td>
<td>50–100</td>
<td>—</td>
<td>1000</td>
<td>1400</td>
<td>960</td>
<td>62</td>
<td>24</td>
<td>14</td>
<td>78</td>
<td>131</td>
<td>116</td>
<td>51</td>
</tr>
<tr>
<td>Ammonia, (\mu)mol/L</td>
<td>&lt;55</td>
<td>—</td>
<td>&gt;286</td>
<td>221</td>
<td>174</td>
<td>156</td>
<td>79</td>
<td>43</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Adjusted Ca, mmol/L(^b)</td>
<td>2.20–2.60</td>
<td>2.21</td>
<td>2.19</td>
<td>2.00</td>
<td>2.17</td>
<td>2.00</td>
<td>2.13</td>
<td>2.04</td>
<td>2.00</td>
<td>2.15</td>
<td>—</td>
<td>2.19</td>
</tr>
<tr>
<td>ionized Ca, mmol/L</td>
<td>1.13–1.32</td>
<td>1.18</td>
<td>—</td>
<td>1.12</td>
<td>1.17</td>
<td>1.12</td>
<td>1.25</td>
<td>1.09</td>
<td>1.04</td>
<td>—</td>
<td>—</td>
<td>—</td>
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<tr>
<td>Osmolality, mOsmol/kg</td>
<td>288–298</td>
<td>300</td>
<td>323</td>
<td>323</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
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<tr>
<td>Glucose, mmol/L</td>
<td>3.5–6.0</td>
<td>2.9</td>
<td>6.9</td>
<td>—</td>
<td>—</td>
<td>5.3</td>
<td>9.2</td>
<td>9.2</td>
<td>6.6</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Albumin, g/L</td>
<td>35–50</td>
<td>44</td>
<td>38</td>
<td>36</td>
<td>39</td>
<td>20</td>
<td>23</td>
<td>23</td>
<td>23</td>
<td>31</td>
<td>34</td>
<td>34</td>
</tr>
<tr>
<td>ALT, U/L</td>
<td>&lt;35</td>
<td>70</td>
<td>60</td>
<td>37</td>
<td>41</td>
<td>22</td>
<td>22</td>
<td>27</td>
<td>27</td>
<td>31</td>
<td>34</td>
<td>33</td>
</tr>
<tr>
<td>Platelets, (\times10^9)/L</td>
<td>150–400</td>
<td>112</td>
<td>92</td>
<td>64</td>
<td>56</td>
<td>19</td>
<td>20</td>
<td>29</td>
<td>36</td>
<td>225</td>
<td>75</td>
<td>48</td>
</tr>
<tr>
<td>APTT, s</td>
<td>23.0–35.0</td>
<td>—</td>
<td>30.6</td>
<td>40.2</td>
<td>34.8</td>
<td>46.0</td>
<td>32.9</td>
<td>28.2</td>
<td>44.8</td>
<td>36.7</td>
<td>25.8</td>
<td>29.6</td>
</tr>
<tr>
<td>PT, s</td>
<td>10–14</td>
<td>15.8</td>
<td>17.2</td>
<td>19.8</td>
<td>18.0</td>
<td>18.5</td>
<td>15.4</td>
<td>14.1</td>
<td>17.8</td>
<td>16.9</td>
<td>15.4</td>
<td>15.5</td>
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<tr>
<td>Lactate, mmol/L</td>
<td>0.5–2.0</td>
<td>4.3</td>
<td>—</td>
<td>6.4</td>
<td>1.7</td>
<td>1.6</td>
<td>1.3</td>
<td>2.1</td>
<td>1.7</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

\(^a\) All analyses were performed on lithium heparin–treated plasma, except for glucose (plasma treated with fluoride and EDTA), full blood count (potassium EDTA), ionized calcium and lactate (whole blood), and APTT and PT (sodium citrate).

\(^b\) Calcium results were adjusted to give an adjusted calcium concentration by means of a formula that includes the measured total plasma calcium concentration and the plasma albumin concentration (40.4 g/L) of the local population. This adjustment compensates for variations in albumin concentration. Routine renal and liver analytes not stated were within reference limits throughout the hospitalization.
then titrated over a 2-week period to 100 mg daily (as an outpatient). The patient was discharged after 32 days.

**DISCUSSION**

In the majority of published cases of VPA overdose, the patient recovers within 24 to 48 h, unlike the patient in this case, in which a GCS of 12 was achieved only by day 7 and the patient was not discharged until day 32. This case of severe acute VPA toxicity highlights a number of biochemical and metabolic features associated with VPA overdose, including hyperammonemic encephalopathy with profound respiratory alkalosis, an increased AG metabolic acidosis, hypernatremia, hypocalcemia, and thrombocytopenia (1).

Other recognized but rare complications of overdose, which were not observed in this case, include heart block, pancreatitis, acute renal failure, alopecia, leukopenia, anemia, and optic nerve atrophy (1).

**HYPERAMMONEMIC ENCEPHALOPATHY**

The encephalopathy observed in this case was a consequence of hyperammonemia caused by reduced cellular glutamate uptake and activation of \( \text{N}-\text{methyl-}\text{D-aspartate receptors} \) (1). The VPA metabolite 2-propyl-2-pentenoic acid, a known neurotoxin, may also have contributed to the encephalopathy.

Raja and Azzoni (2) found a positive correlation between VPA and the plasma ammonia concentration; however, hyperammonemia has been observed at both therapeutic and supratherapeutic VPA concentrations, implying that other factors may contribute to the development of hyperammonemia and therefore should be considered in the differential diagnosis. These factors include polypharmacy (e.g., phenytoin), liver disease, and underlying genetic disorders of the urea cycle or carnitine metabolism (3). Moreover, some data suggest that preexisting carnitine deficiency or VPA-induced deficiency may contribute to hyperammonemic encephalopathy (4).

The patient had a low GCS for several days after admission, despite total VPA concentrations within the normal therapeutic window. This low GCS may have been due to the accumulation of the neurotoxic VPA metabolite 2-propyl-2-pentenoic acid or free VPA. In a previous case (5), in which the total VPA concentrations fell below the therapeutic interval, the patient still had a low GCS, but with an increased free VPA concentration. Measurement of free VPA may be useful in patients with unexplained altered cognition.

**HEPATOTOXICITY**

Interestingly, the patient did not demonstrate any overt signs of hepatotoxicity. Liver function tests showed only mild derangement at admission (Table 1). Serum transaminase activity is increased in 30%–50% of patients after a VPA overdose (6). Such a change is dose-dependent type I hepatotoxicity and is often transient. In contrast, type 2 hepatotoxicity is a rare, potentially fatal side effect of VPA treatment and occurs weeks to months after initial exposure. It is thought to be due to mitochondrial dysfunction or to a disturbance in fatty acid metabolism. Mechanisms that have been proposed for type 2 hepatotoxicity include (a) reactive VPA metabolites (e.g., 2-propyl-4-pentenoic acid), (b) carnitine deficiency, (c) drug-induced CoA deficiency, (d) hyperammonemia, (e) familial metabolic defects, and (f) oxidative stress (6). Discontinuation of VPA treatment has been recommended if transaminases increase to >3 times the upper limit of normal (7).

**HYPERNATREMIA**

The hypernatremia observed in this patient is thought to have been due to the Na\(^{+}\) present in the VPA preparation. The fact that 100 mg VPA contains an estimated 13.2 mg of Na\(^{+}\) likely explains the observed hypernatremia. This case is consistent with one described in a previous publication (8), in which hypernatremia (Na\(^{+}\) >145 mmol/L) was observed more frequently (5 of 27) in patients with peak VPA concentrations >450 mg/L than in patients with peak VPA concentrations <450 mg/L (2 of 81 patients).

**AG ACIDOSIS**

The increased AG observed in this case is likely to have been due to the VPA along with lactic acidosis, which is thought to have been due to circulatory compromise. Chang and Abbott (6) reported an increased AG (>15 mmol/L) in 26% of patients with VPA concentrations >450 mg/L (those with VPA concentrations <450 mg/L did not have an increased AG). It is important to consider other unmeasured anions when faced with an increased AG, especially in an overdose case. Other potential anions include ketoacids (\( \beta\)-hydroxybutyrate and acetoacetate), which are observed in diabetic or alcoholic ketoacidosis, and formic and oxalic acid (observed in methanol and ethylene glycol poisoning, respectively).

**HYPOCALCEMIA**

Mild hypocalcemia was also observed in this case. Unlike phenytoin, which inhibits vitamin D hydroxylation, VPA does not interfere with vitamin D metabolism. VPA metabolites have been proposed to act as anions, thus binding plasma calcium ions and causing hypocalcemia (9), and presumably lowered ionized calcium concentrations. The alkalosis in this case is thought to have contributed to lowering the ionized calcium concentration (Table 1).
THROMBOCYTOPENIA
The marked thrombocytopenia observed in the presented case is a well-recognized feature of VPA toxicity and is due to bone marrow suppression. Thrombocytopenia typically occurs when VPA concentrations are >450 mg/L (10).

ROLE OF CARNITINE IN THE TREATMENT OF VPA TOXICITY
The patient was given carnitine (plasma carnitine was not measured). Although the evidence for its use is largely anecdotal, L-carnitine is recommended for patients with acute VPA overdose who demonstrate a decreased level of consciousness, hyperammonemia, or VPA concentrations >450 mg/L (1). VPA is normally metabolized by the liver via glucuronic acid conjugation, mitochondrial β-oxidation, and cytoplasmic ω-oxidation (Fig. 1). In healthy individuals, β-oxidation is the predominant pathway used, as opposed to the ω-oxidation pathway, and the metabolites are relatively nontoxic. VPA used in long-term/high-dose therapy or after acute VPA overdose leads to increased ω-oxidation, which produces toxic metabolites (e.g., 2-propyl-4-pentenoic acid and propionic acid metabolites). The role of carnitine is in facilitating the transport of long-chain fatty acids from the cytosol into the mitochondria for β-oxidation to produce acetyl-CoA for the Krebs cycle. The transport enzymes known collectively as the “carnitine shuttle” (Fig. 1) are also used in VPA metabolism, so any depletion of carnitine—whether by reduced endogenous biosynthesis, dietary intake (rare in well-nourished individuals), or reduced tubular reabsorption—will affect VPA metabolism.

Fig. 1. Hepatocellular metabolism and transport (“carnitine shuttle”) of VPA.
4-en-VPA, 2-propyl-4-pentenoic acid; ACoAS, acyl-CoA synthetase; CPT1, carnitine palmitoyl transferase 1; CT, carnitine translocase; 2-en-VPA, 2-propyl-2-pentenoic acid. Adapted from Lheureux and Hantson (1).

POINTS TO REMEMBER
• Severe acute VPA toxicity may be characterized by several biochemical abnormalities, including hyperammonemia, hypernatremia, hypocalcemia, an increased osmolal and anion gap, respiratory alkalosis, metabolic acidosis, and increased transaminase activity.
• Altered cognitive function may be observed in patients who have ingested a VPA overdose, even when total VPA concentrations are within or below the normal therapeutic window. This symptom may be due to the accumulation of the neurotoxic VPA metabolite 2-propyl-2-pentenoic acid.
• VPA-induced hyperammonemia has been proposed to be mediated by carnitine deficiency; thus, L-carnitine supplementation may prevent or attenuate hyperammonemia.
Clinical Case Study

Author Contributions: All authors confirmed they have contributed to the intellectual content of this paper and have met the following 3 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; and (c) final approval of the published article.

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References


Commentary

Jonathan H. Pincus*

Valproic acid was cleared by the US Food and Drug Administration in 1978 as an antiepileptic. In 1995, it was cleared for use in treating mania, an indication that led to a corresponding expansion of cases of overdose.

Valproate impairs fatty acid metabolism and depletes carnitine, thereby inducing a kind of mitochondrial defect. It also interferes with the urea cycle, increasing ammonia concentrations. Infusion of carnitine has become part of the accepted treatment for valproate overdose, although no controlled studies of the effectiveness of this treatment have been completed.

Valproic acid commonly causes asymptomatic increases in ammonia and amylase/lipase. The routine checking of these analytes is unnecessary and not recommended, but if symptoms such as nausea, vomiting, and confusion occur—with or without tremor, asterixis, or abdominal pain—it may be reasonable to measure serum ammonia and pancreatic enzymes. When pancreatitis is suspected, serum calcium should be measured to rule out hypocalcemia caused by the formation of calcium salts.

Valproate is extraordinarily safe when blood concentrations are within the therapeutic interval (50–100 μg/mL) and even when concentrations are increased to as high as 350 μg/mL in persons without accompanying symptoms. Laboratory findings alone are not sufficient reasons to alter therapy, especially if valproate seems to be helping.

At toxic concentrations, valproate can induce fatal hepatic failure that resembles Reye syndrome, or it can induce fatal pancreatitis. When blood concentrations of the drug exceed 500 μg/mL, consciousness is usually affected. When concentrations approach 800 μg/mL, a coma requiring intubation is usually present. Note that enteric-coated forms cause delayed and prolonged coma, justifying vigorous gastric lavage.

Suicide attempts cause an acute illness. When the serum calcium concentration is low, pancreatitis with calcium salt formation in abdominal fat should be suspected. When suicide is likely to have been attempted, amylase/lipase must be measured. A marked increase in serum ammonia is usually accompanied by hyperventilation and respiratory alkalosis; thus, the pH can be misleading because lactic acidosis can be due to mitochondrial failure.

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