Valproic Acid Intoxication

October 4, 2020 by Josh Farkas

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pharmacology & pathophysiology

formulations and absorption
• Valproic acid is available in immediate-release, delayed-release (q12-hr administration) or extended-release (q24-hr administration) forms.
• In the context of overdose, absorption may be considerably delayed (with peak levels delayed for up to about a day after ingestion, especially for extended-release formulations).

protein binding & distribution in the body

• Valproic acid has a relatively small volume of distribution (close to the extracellular volume).
• At therapeutic levels, valproic acid is >80% bound to albumin.
• At toxic levels (e.g., >150 mcg/ml or >1,050 uM/L), protein binding is saturated and the fraction of free drug in the blood increases substantially. This may explain why neurologic symptoms start emerging around these levels.
  • The free drug is responsible for tissue toxicity (rather than the total level in the blood).

metabolism in the liver via four pathways

• (a) Glucuronic acid conjugation (50%)
  • This is probably the most desirable metabolic pathway to follow, yielding nontoxic metabolites excreted in the bile.
• (b) Beta oxidation in the mitochondria (40%)
  • This may deplete intracellular acetyl-CoA, so it’s not fantastic.
• (c) Omega oxidation in the cytosol (10%) 😒
  • This is generally a minor pathway, but may increase in the context of overdose. Additionally, a relative carnitine deficiency may promote omega oxidation.
  • Omega oxidation yields toxic metabolites:
    • 2-propyl-2-pentenoic acid (2-EN-VPA) may cause cerebral edema.
    • 2-propyl-4-pentenoic acid (4-EN-VPA) may cause hepatotoxicity.
    • Propionic acid metabolites may precipitate hyperammonemia.
• (d) Some valproate gets conjugated to carnitine (VPA-carnitine), which may be renally excreted.
  • This doesn’t seem to be a clinically important mechanism of valproic acid clearance. However, this pathway may lead to carnitine depletion – which may be clinically problematic.
  • VPA-Carnitine may also inhibit carnitine uptake into the cells – further exacerbating intracellular carnitine deficiency.
  • The normal half-life of valproic acid is ~5-20 hours. However, in the context of intoxication this may double. Metabolism is also slower in patients with hepatic dysfunction.

clinical manifestations

neurological

• Neurologic abnormalities are the primary manifestation of toxicity. These may range from sedation to coma. There are numerous causes of these changes (including direct effects from valproate, consequences of hyperammonemia, and cerebral edema).

  • Hyperammonemic encephalopathy
    • May cause obtundation and seizures (with the potential to progress to coma and death).

  • Cerebral edema with herniation can occur.
    • Appears to relate to levels of ammonia and the valproic acid metabolite 2-propyl-2-pentenoic acid (rather than valproic acid itself).
    • Usually occurs ~2-3 days after ingestion, despite improvements in valproic acid levels.

  • Other neurological manifestations may include agitation, tremor, myoclonus, nystagmus, and miosis.

gastrointestinal

• Nausea, vomiting, and diarrhea are common symptoms.
• Mild hepatitis can be seen.
• Pancreatitis may rarely occur.

cardiovascular

• Hypotension, tachycardia, and shock may occur.
- Heart block is rarely seen.
- Drug-induced Brugada pattern may occur.
- EKG findings may rarely simulate myocardial ischemia.

**laboratory tests & amount of valproate ingested**

**quantity of valproate ingested**

- The therapeutic daily dose of valproic acid is up to 60 mg/kg/day (e.g., ~4 grams).
- <200 mg/kg ingestion (e.g., ~15 grams) is usually mild or asymptomatic.
- 200-400 mg/kg ingestion (e.g., ~15-30 grams) is likely to cause some degree of reduced consciousness.
- >800 mg/kg ingestion (e.g., >~60 grams) may be considered massive, with increased risk of multiorgan failure.
- Occasional patients may have underlying genetic urea cycle disorders, which substantially increases the risk of hyperammonemic encephalopathy.

**serum valproic acid level**

- 50-100 mg/L (350-700 uM/L): Therapeutic level.
- Level >180 mg/L (1,260 uM/L): Usually corresponds to some mental status impairment.
- Level >450 mcg/ml (>3120 uM/L): Serious intoxication is likely; indication for IV L-carnitine; non-lactic metabolic acidosis can occur.
- Level >850 mg/L (>5900 uM/L): May correlate with severe intoxication (e.g., coma).
- Level >900 mg/L (>6,250 uM/L): Weaker indication to initiate dialysis.
- Level >1300 mg/L (>9,000 uM/L): Stronger indication to initiate dialysis.
- Absorption may be delayed, so levels should be cycled q2-q4hrs to peak. The initial level upon admission can be normal, with delayed emergence of toxicity.
- You may need to ask the laboratory to dilute the specimen, in order to quantify the actual drug level.

**ammonia level**

- Normal level is <80 mcg/dL (47 umol/L).
- Chronic valproic acid therapy can be associated with moderate hyperammonemia (e.g., ~ 100-400 mcg/dL).
- Severe valproic acid poisoning is almost always associated with some elevation in ammonia level. ([25950372](https://pubmed.ncbi.nlm.nih.gov/25950372/))
- Markedly elevated levels may correlate with an increased risk of cerebral edema.

**other laboratory derangements which may occur**

- Elevated anion gap metabolic acidosis (AGMA) – due to a combination of ketoacids, propionic acid, carboxylic acid, lactate, and valproic acid itself.
- Elevated transaminase levels.
- Hypernatremia (due to the sodium content of valproic acid) or hyponatremia (due to valproic acid induced SIADH).
- Hypocalcemia.
- Cytopenias may emerge 3-5 days after a massive overdose, due to bone marrow suppression. Any cell line may be affected, but thrombocytopenia seems to be a particular issue.

**imaging**

**ocular ultrasonography**

- May be used as a screening test to detect cerebral edema.
- Exact performance in this context is unknown, however.

**head CT scan**

https://emcrit.org/ibcc/vpa/
Potential indications may include:
- Possible head trauma with risk for intracranial hemorrhage
- Clinical concern regarding cerebral edema

**general supportive measures**

- **Intubation** may be needed for airway control.
- **Seizures** may be managed in the usual fashion
  - Benzodiazepines are the front-line therapy.
  - More on the management of seizures and status epilepticus [here](https://emcrit.org/ibcc/status-epilepticus/).
- Electrolyte management of hypernatremia [here](https://emcrit.org/ibcc/hypernatremia/) and hypocalcemia [here](https://emcrit.org/ibcc/hypocalcemia/).
- **Aspirin** should be discontinued or avoided (aspirin may increase the free levels of valproic acid, due to competition for binding to albumin).

**gastrointestinal decontamination**

**background information**

- Large overdose can cause delayed absorption of valproic acid from the gut, with levels peaking in a delayed fashion (up to 24 hours after the ingestion). This phenomenon is particularly notable for patients taking extended-release formulations.
- Ongoing absorption from the gut for a protracted period of time implies that there may be utility in techniques to limit absorption.
- There is no high-quality evidence supporting the use of gastrointestinal decontamination in valproic acid toxicity.
- Valproic acid can be removed via hemodialysis, so decontamination isn't mandatory in the context of immediate access to hemodialysis. However, even if there is access to hemodialysis, decontamination could still have some potential roles:
  - (i) Decontamination might avoid the requirement for hemodialysis (which is invasive and expensive).
  - (ii) Decontamination might limit the duration of hemodialysis required. Even at a dialysis center, maintaining a patient on continuous high-intensity hemodialysis can be a bit challenging (e.g., regarding staffing and also clotting of the dialysis filter).

**activated charcoal**

- Consider this for patients who present within 2-4 hours and are able to protect their airway.
- Do not intubate or place a nasogastric tube for the purpose of administering charcoal.

**whole bowel irrigation**

- Bowel irrigation may be considered for patients who are intubated due to depressed mental status, following a large ingestion of sustained-release or extended-release formulations.
- Valproic acid itself will slow gastric motility, so whole bowel irrigation may be most likely to succeed if initiated immediately following intubation (when drug levels are still relatively low).
- Bowel irrigation may be accomplished by administering an isotonic solution of polyethylene glycol (i.e., ‘GoLytely’) via an orogastric tube, beginning at a rate of 1.5-2 liters/hour. If emesis occurs, reduce the rate by 50%. Continue until effluent is clear (just as you would for a colonoscopy prep). If the patient received a dose of charcoal, passage of charcoal per rectum may also be a sign of adequate evacuation.

**naloxone**

- The efficacy of naloxone in reversing CNS depression in this situation is debatable. Mechanistically, valproate may cause somnolence by inhibiting the reuptake of GABA (and thereby potentiating GABA signaling in the brain). Naloxone has been demonstrated to reverse this blockade in vitro, creating a plausible mechanism wherein naloxone could antagonize valproate-induced sedation.
- A handful of case reports describe efficacy from naloxone in mild-moderate intoxications (table below). However, it’s difficult to exclude the possibility of occult co-intoxication with opioids. Naloxone fails in more serious intoxications.
Valproic Acid Intoxication - EMCrit Project

- Naloxone administration is reasonable in patients with mild-moderate intoxication. However, for patients who clearly have a severe intoxication, naloxone administration should not delay more definitive and evidence-based therapies (e.g., intubation and hemodialysis).

<table>
<thead>
<tr>
<th>Author</th>
<th>PI/Age</th>
<th>Serum VPA</th>
<th>Naloxone</th>
<th>Response/Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steinman et al (19)</td>
<td>19 mo</td>
<td>185 ug/mL</td>
<td>0.01 mg/kg</td>
<td>Coma reversed in 3 minutes, lethargy 20 minutes later was reversed with 2nd equal dose, no further relapse, survived</td>
</tr>
<tr>
<td>Connacher et al (32)</td>
<td>Adult</td>
<td>2,877 ug/mL</td>
<td>0.8 mg</td>
<td>No response, patient died</td>
</tr>
<tr>
<td>Mortensen et al (20)</td>
<td>Adult</td>
<td>2,120 ug/mL</td>
<td>0.02 mg</td>
<td>No response, survived</td>
</tr>
<tr>
<td>Alberto et al (20)</td>
<td>Adult</td>
<td>180.4 ug/mL</td>
<td>2.0 mg</td>
<td>Somnolence and respiratory depression reversed without relapse, survived</td>
</tr>
<tr>
<td>Montero et al (21)</td>
<td>Adult</td>
<td>487.8 ug/mL</td>
<td>0.4 mg</td>
<td>Coma reversed within 1-2 mins, relapse in 20 mins was reversed with 0.8 mg naloxone and 0.42 mg/hr naloxone infusion 24 hours without further relapse, survived</td>
</tr>
<tr>
<td>Andersen et al (5)</td>
<td>Adult</td>
<td>1,440,000 ug/mL</td>
<td>Not recorded</td>
<td>No response, survived</td>
</tr>
<tr>
<td>Present case</td>
<td>Adult</td>
<td>138 ug/mL</td>
<td>2.0 mg</td>
<td>Obtundation reversed within one minute, somnolence in one hour reversed with 2.0 mg naloxone without further relapse, survived</td>
</tr>
</tbody>
</table>

- Carnitine physiology

- Metabolism of valproic acid via beta-oxidation in the mitochondria causes carnitine depletion (explored further above).
- Consequences of carnitine deficiency:
  - i) Inability to metabolize valproic acid via beta-oxidation (which indirectly increases omega-oxidation, producing more toxic metabolites).
  - ii) Carnitine is required for the metabolism of fatty acids. Thus, carnitine deficiency may cause intracellular accumulation of fatty acids, with a subsequent deficiency of energy substrates (such as acetyl-CoA metabolites). One consequence of this is impairment of the urea cycle, exacerbating hyperammonemia.

- Potential indications for carnitine

- Possible indications for IV carnitine:
  - Moderate to severe hyperammonemia
  - Valproate level >450 mcg/ml (>3120 uM/L)
  - Reduced level of consciousness
  - Severe hepatotoxicity
- Indications for oral carnitine: Patients with valproate intoxication who don't meet the above indications for intravenous therapy.
- Carnitine administration appears to be quite safe, so when in doubt this should be given.

- Dose of IV carnitine

- Loading dose 100 mg/kg IV over 30 minutes (maximal dose of 6 grams) infused over 30 minutes.
- Maintenance dose of 50 mg/kg IV (maximum dose 3 grams) q8hrs.
- Repeating the loading dose may be considered in patients undergoing hemodialysis.
- When to stop IV carnitine isn't entirely clear. It may be reasonable to continue carnitine until the patient has improved clinically, valproate concentrations are at a therapeutic level, and ammonia levels have normalized.

- Oral carnitine

- ! Oral bioavailability is low, so oral administration of carnitine is reserved for patients who are not critically ill.
- The dose is 100 mg/kg per day (up to 3 grams) in 3-4 divided doses (e.g., typically 990 mg PO q8hr).
- Patients who deteriorate clinically may meet criteria to transition to IV carnitine (see indications above).

- Hemodialysis
general

- No controlled study has been performed on the use of hemodialysis. However, case series demonstrate that hemodialysis dramatically reduces the half-life for valproic acid elimination. Hemodialysis can reduce the half-life to ~2 hours, so ~4-8 hours of hemodialysis might be adequate to reduce valproate levels substantially.
- Given that valproic acid can cause irreversible neurotoxicity, hemodialysis seems justified in severe cases.
- Hemodialysis will also directly remove ammonia, thereby improving hyperammonemic encephalopathy and ammonia-driven elevation of intracranial pressure.
- Valproic acid is cleared via hepatic metabolism (not the kidneys). Therefore, the patient's renal function is not relevant to the decision regarding whether or not to dialyze.

indications

- The following are the EXTRIP workgroup's expert guidance on when to perform hemodialysis. Indications were classified as "recommended" (more strongly indicated) or "suggested" (less strongly indicated). ([25950372](https://pubmed.ncbi.nlm.nih.gov/25950372/))

  - **[1] Valproic acid level**
    - >1,300 mg/L (>9,000 uM/L) – dialysis recommended
    - >900 mg/L (>6,250 uM/L) – dialysis suggested
  
  - **[2] CNS dysfunction**
    - Cerebral edema – dialysis recommended
    - Coma or respiratory depression requiring intubation – dialysis suggested
    - Acute hyperammonemia – dialysis suggested (this is a bit fuzzy and requires some clinical judgement, since mild hyperammonemia can occur with mild-moderate valproate intoxication)

  - **[3] Shock & acidosis**
    - Shock – dialysis recommended
    - pH < 7.1 – dialysis suggested

mode of dialysis & when to discontinue

- Intermittent hemodialysis is preferred to maximize removal of valproic acid.
  - Even if the patient is in shock, hemodialysis is still preferred (with no net ultrafiltration, i.e. the patient should be "run even"). Shock is likely due to valproic acid, so the shock may not resolve until after initiation of hemodialysis.
  - Continuous renal replacement therapy is not very effective for valproic acid removal.

- When to discontinue dialysis is unclear. EXTRIP recommends continuing dialysis until there is clinical improvement and the valproate level is within a therapeutic range discontinuation (e.g., <100 mg/L or <700 uM/L). ([25950372](https://pubmed.ncbi.nlm.nih.gov/25950372/))

- Rebound elevation in valproate level can occur after cessation of dialysis, but this generally doesn't lead to clinically significant toxicity. Thus, valproate and ammonia levels probably should be followed after stopping dialysis.

carbapenems

Carbapenems reduce valproic acid levels by ~50-80% (when both are used at therapeutic doses). Consequently, co-administration of these agents is usually contraindicated, to avoid therapeutic failure of valproic acid.

- The primary explanation for this drug interaction seems to be a reduction in entero-hepatic circulation of valproic acid.
  - Normally, valproate is metabolized largely in the liver into valproate glucuronide. Valproate glucuronide is a harmless metabolite which is secreted into the bile. In the intestine, valproate glucuronide may be metabolized back into valproic acid by acylpeptide hydrolase – which is then absorbed into the blood.
  - Carbapenems inhibit acylpeptide hydrolase, thereby reducing entero-hepatic circulation of valproate.

Another possible explanation for this interaction may be increased distribution of valproate into erythrocytes. ([29733112](https://pubmed.ncbi.nlm.nih.gov/29733112/))

physiology

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clinical utility

https://emcrit.org/ibcc/vpa/
Some case reports have suggested successful use of meropenem to accelerate valproic acid clearance.

Use of carbapenems remains controversial, but this may be reasonable (especially among patients who have an indication for antibiotic therapy, for example aspiration pneumonia).

Both ertapenem and meropenem appear equally effective in accelerating valproate metabolism. Imipenem is less effective in reducing valproate metabolism, so it may not be helpful.

More on dosing of carbapenems here.

**additional treatments for hyperammonemia**

**hyperammonemia physiology**

- **Mechanisms of ammonia elevation:**
  - (1) Valproic acid and metabolites (especially propionic acid) inhibit the activity of N-acetylglutamate synthetase (NAGS). Reduced N-acetylglutamate decreases the activity of carbamoyl phosphate synthetase I. Carbamoyl phosphate synthetase is a key enzyme in the urea cycle, so impairment leads to urea cycle dysfunction with ammonia accumulation.
  - (2) VPA itself may inhibit carnitine (a required cofactor for long-chain fatty acid metabolism). Carnitine deficiency can theoretically cause hyperammonemia, but in practice this seems to be a less important mechanism (especially among patients being treated with IV carnitine).

 ammonia is toxic to the brain, with the potential to cause cerebral edema and herniation. Unfortunately, there's no specific cutoff value regarding how much ammonia is safe.

For patients with valproic acid poisoning and hyperammonemia, some additional therapies directed at this component of the intoxication might be beneficial.

**nutritional support with IV dextrose**
Inadequate glucose intake may trigger gluconeogenesis, which involves endogenous protein catabolism. Protein catabolism places a greater metabolic stress on the urea cycle, potentially increasing the production of ammonia (figure above). Therefore, glucose administration is commonly a component of managing patients with urea cycle disorders.

Administration of \(~2-3\) g/kg glucose per day \((\sim100-150\) grams/day\) might suppress gluconeogenesis.[20049080](https://pubmed.ncbi.nlm.nih.gov/20049080/) This is equivalent to roughly:

- D10W (10% dextrose) at a rate of \(\sim50\) ml/hour. D10W is the highest concentration which is typically administered via a peripheral IV line.
- D20W (20% dextrose) at a rate of \(\sim25\) ml/hour.

For patients with hypernatremia due to valproic acid intoxication, the water provided with IV dextrose would be beneficial. For patients with cerebral edema, large volumes of water are undesirable. In that situation, D50W might be preferable (e.g., one 50-ml ampule of D50W every six hours).

Withholding protein administration in the acute phase of a valproic acid ingestion may be sensible (at least until the ammonia levels are controlled).

**Hemodialysis**

- Hemodialysis might be the most effective therapy overall for valproic acid-induced hyperammonemia (since it removes ammonia, valproic acid, and perhaps some of the valproate metabolites).
- Hyperammonemic encephalopathy is an indication for dialysis ([hemodialysis](#hemodialysis)), (more on this above).

**Intravenous L-arginine**

- Arginine may activate N-acetylglutamate synthetase (NAGS), thereby counterbalancing the inhibitor effect of valproic acid metabolites.
- L-arginine is an amino acid, making it generally safe (although it may decrease the pH somewhat).
- Unlike L-carnitine, L-arginine is not a standard component of therapy for valproic acid intoxication. However, one case series demonstrated that L-arginine administration correlated with improvements in hyperammonemia.[28152637](https://pubmed.ncbi.nlm.nih.gov/28152637/)

IV L-arginine could be a reasonable consideration in the following situations:

- i) Moderate to severe hyperammonemia, without immediate access to hemodialysis
- ii) Persistent hyperammonemia, despite hemodialysis
- iii) Hyperammonemia which poses an immediate threat to life (e.g., moderate to severe hyperammonemia with evidence of cerebral edema)

A reasonable dose may be [22642880](https://pubmed.ncbi.nlm.nih.gov/22642880/)

- Loading bolus of 250 mg/kg (1.2 mM/kg) over 2 hours.
- Maintenance infusion of 250 mg/kg/day (1.2 mM/kg/day).

**Case series demonstrating correlation of L-arginine use with control of hyperammonemia**

![Case series demonstrating correlation of L-arginine use with control of hyperammonemia](https://emcrit.org/ibcc/vpa/attachment/argininevpa/)

https://emcrit.org/ibcc/vpa/
serial re-assessment

- Follow neurologic status to detect any signs of ICP elevation
- Follow serial labs (including electrolytes, valproic acid level, and ammonia level). These should be cycled q2-4 hours initially.

for patients on valproate to manage epilepsy

- Reduction in valproic acid levels below a therapeutic level may increase the risk of seizure.
- As valproic acid levels begin to fall below a therapeutic level, either:
  - (1) An alternative and safer anti-epileptic agent may be added
  - (2) Valproic acid may need to be re-started

summary

[Labs to obtain](https://emcrit.org/?attachment_id=478635)

- Electrolytes including Ca/Mg/Phos, liver function tests, creatinine kinase
- Ammonia level & Valproic acid level

**Toxic dose (very roughly!):**

- >200 mg/kg (~15 grams) usually causes some mental status impairment.

**Serum valproate levels:**

- 50-100 mg/L (350-700 uM/L): Therapeutic level
- >180 mg/L (1,260 uM/L): Usually corresponds to Δ mental status.
- >450 mcg/ml (>3120 uM/L): Indication for IV L-carnitine.
- >850 mg/L (>5900 uM/L): May correlate with coma.
- >900 mg/L (>6,250 uM/L): Possible indication to initiate dialysis.

**Treatment:**

- Activated charcoal (if <2-4 hours post ingestion & protecting airway).
- Intubation if needed to protect airway. If intubation is performed, then whole bowel irrigation may be considered among intubated patients who ingested extended-release or sustained-release tablets (but don’t intubate for this reason).
- Naloxone may be considered to improve mental status.
- Meropenem or ertapenem may be considered in moderate/severe cases to accelerate metabolism.
- Avoid aspirin.

**L-Carnitine**

- Indications for IV carnitine: Hyperammonemia, valproate level >450 mcg/ml (>3,120 uM/L), consciousness, hepatotoxicity.
- If no indication for IV L-carnitine, consider oral L-carnitine.

**Potential indications for dialysis**

- Valproic acid level >900 mg/L (>6,250 uM/L)
- Cerebral edema or acute hyperammonemic encephalopathy
- Coma or respiratory depression requiring intubation
- Shock or pH <7.1

**Additional treatments that may be considered in hyperammonemia**

- Intravenous dextrose to suppress gluconeogenesis.
- L-arginine (if hyperammonemia severe/refractory)
A normal valproic acid level upon admission doesn't exclude severe valproic acid toxicity. If suspicion for a significant ingestion exists, repeat levels are needed. Nephrology should be involved early to consider hemodialysis. Attention should be paid to both valproic acid levels and ammonia levels. Both substances are potentially toxic. These two levels may not track in parallel (e.g., a patient with underlying urea cycle abnormalities could develop severe hyperammonemia without having severely elevated valproic acid levels). Watch for the development of elevated intracranial pressure (however, aggressive management of valproate and ammonia levels will ideally prevent this).

**Going further:**

- **A Toxicological brain teaser: The complexities of valproic acid metabolism** [Tox & Hound, by Christine Murphy]

**references**


