Levocarnitine for Acute Valproic Acid Overdose: Breaking the Link Between Hyperammonemia and Altered Mental Status

Patrick Aaronson Pharm.D.
Clinical Pharmacist – Emergency Medicine
University of Florida and Shands
Florida/USVI Poison Information Center
Jacksonville

Objectives

1. Evaluate and characterize hyperammonemia in the setting of acute valproic acid (VPA) toxicity.

2. Describe the potential risks and benefits of utilizing levocarnitine in acute VPA toxicity.
Conflict of Interest

Disclosures

• The authors declare that they have no competing interests.

• All authors of this presentation have nothing to disclose concerning possible financial or personal relationships with commercial entities.

Emergency Department Case

• 28 y/o M presented to the ED after being assaulted

• PMH: Schizophrenia

• Became increasingly difficult to arouse

• Nonconvulsive seizures were suspected
  – EEG: mild encephalopathy

• Valproic acid 1000 mg IV was administered
**Incidence**

- Poison Centers nationwide receive ~ 9000 inquiries annually for VPA exposures
- ~ 2000 exposures treated in health care facility
- ~ 450 exposures have moderate to severe outcomes
- Ahead of its 1st generation counterparts
  - Phenytoin
  - Carbamazepine
- Psychiatric patients

**Acute VPA Complications**

**Rare**

- Hepatotoxicity
- Hemorrhagic pancreatitis
- Acute respiratory distress syndrome
- Acute renal failure

**Most common**

- CNS depression
Acute VPA Toxicity

- CNS depression is the most common manifestation:
  - Mild drowsiness (majority)
  - Profound coma → fatal cerebral edema

- VPA [plasma] > 450 mg/L
  - Moderate to major side effects

- VPA [plasma] > 850 mg/L
  - Metabolic acidosis, ventilation, and coma

- Cerebral edema: 12h – 4 days

Hyperammonemia and Encephalopathy

\[ \text{NH}_3 + \text{Glutamate} \rightarrow \text{Glutamine} \]

\[ \text{Glutamine Synthetase} \]

\[ \text{Glutaminase} \]

Blood Brain Barrier

References:
- Clin Toxicol 2009;47:101-111
- Neurochem Int 2002;42:123-142
- Biochem Pharm 2010;80:1303-1308
VPA-induced Hyperammonemic Encephalopathy

Hyperammonemia

• Asymptomatic: 50% of patients with chronic VPA therapy
  – Pediatric and psychiatric

• Significant Encephalopathy
  – Unknown incidence of hyperammonemia in acute VPA toxicity
  – Impaired Consciousness
  – ↑ Seizure frequency

Arch Neurol 1982;39:591-592
Neurology 1984;34:550-553

Pathogenesis of Hyperammonemia: VPA Toxicity

Fatty Acid

\[
\begin{align*}
\text{VPA + Carnitine} & \rightarrow \text{ω - oxidation} \\
\text{VPA - CoA} & \rightarrow \text{4-enol-VPA} \\
\text{2-enol-VPA - CoA} & \rightarrow \text{Mitochondria} \\
\text{CO}_2 & \rightarrow \text{NH}_3 \\
\text{CPS I} & \rightarrow \text{Urea} \\
\text{Hepatic Cell} & \rightarrow \text{Renal Excretion}
\end{align*}
\]

Adapted: Goldfrank’s Toxicologic Emergencies, 8th edn. 2006: 737-739
Correlation between Mental Status and ↑ VPA, ↑ NH₃

↑ VPA : ↑ NH₃ (correlation)
↑ NH₃ : ↓ Carnitine (correlation)
  - J Pediatr 1983;101:782-785

Encephalopathic severity : ↑ NH₃ (no known correlation)
  - J Pediatr 1993;123:318-320

Management of VPA toxicity

- Largely Supportive
  - Mechanical ventilation
- Multi-dosed activated charcoal
- Hemodialysis
  - > 300 mcg/ml, 35% protein bound
- IV levocarnitine
  - 8 anecdotal case reports
  - Expert opinion
Role of Levocarnitine

• Essential for proper metabolism of VPA through β-oxidation
  – ↓ toxic metabolites of VPA from ω-oxidation

• Reactivate the urea cycle
  – Normalize ↑ NH₃ levels

• Binding to VPA
  – Enhanced elimination of VPA through urinary excretion

Levocarnitine: Safety

3 years of poison center data (251 doses of IV levocarnitine)

• Common side effects:
  – Generally safe and well tolerated
  – Fishy odor
  – Mild gastrointestinal upset (oral)

• No known cases of allergic adverse reactions
• Seizures have been reported (no references)
• No known contraindications
Levocarnitine: What is the Evidence?

• Carnitine in the treatment of VPA toxicity (Review)
  – Clin Toxicol 2009;47:101-111
  – Crit Care 2005;9:431-440
  – Ann Pharmacother 2010;44:1287-1293

• Anecdotal Case Reports (8)
  – Epilepsia 1996;37:687-689
  – Hum Exp Toxicol 2007;26:967-969
  – Ann Fr Anesth Reanim 2004;23:357-360

Summary of Case Reports: Levocarnitine for VPA toxicity

<table>
<thead>
<tr>
<th>Age</th>
<th>VPA Peak mg/L</th>
<th>NH3 Peak µmol/L</th>
<th>Recovered LOC</th>
<th>L-Carnitine Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>16 m M</td>
<td>1316</td>
<td>NR</td>
<td>4 days</td>
<td>100 mg/kg, 250 mg IV q8h</td>
</tr>
<tr>
<td>15 m M</td>
<td>1316</td>
<td>49</td>
<td>3 days</td>
<td>100 mg/kg NG daily</td>
</tr>
<tr>
<td>29 y/o F</td>
<td>337</td>
<td>200</td>
<td>3 days</td>
<td>100 mg/kg NG daily</td>
</tr>
<tr>
<td>36 y/o M</td>
<td>560</td>
<td>NR</td>
<td>2 days</td>
<td>50 mg/kg daily route NR</td>
</tr>
<tr>
<td>50 y/o F</td>
<td>288</td>
<td>74</td>
<td>30 hours</td>
<td>1 g IV q8h</td>
</tr>
<tr>
<td>19 y/o M</td>
<td>950</td>
<td>65</td>
<td>2 days</td>
<td>3 g IV q8h</td>
</tr>
<tr>
<td>41 y/o M</td>
<td>1308</td>
<td>NR</td>
<td>36 hours</td>
<td>NR</td>
</tr>
<tr>
<td>23 y/o F</td>
<td>1159</td>
<td>226</td>
<td>NR</td>
<td>100 - 200 mg/kg IV q8h</td>
</tr>
</tbody>
</table>

LOC: level of consciousness; NG = nasogastric; NR = Not reported
Adapted: Ann Pharmacother 2010;44: 1287-1293
IV Levocarnitine: Dose?

- Wide Variation in doses and routes have been used
- Carnitor® package insert:
  - 50 - 100 mg/kg IV for metabolic disorders
  - Not to exceed 6 grams daily oral in adults
    - 15% bioavailability
- Recommendation:
  - 100 mg/kg bolus or infusion load, then
  - 50 mg/kg IV every 8 hours

Carnitor [Package Insert]. 2007
Ann of Pharmacother 2010;44:1287-1293

Utilization of IV Levocarnitine: Retrospective Evaluation and Comparison in Acute Valproic Acid Toxicity

CLINICAL TOXICOLOGY 2010;48(6):646 [ABSTRACT 204]
Purpose / Rationale

(H₀): There is no benefit of using IV levocarnitine in acute VPA toxicity

- Potential advantages of IV levocarnitine therapy:
  - Rapid reversal of acute hyperammonemia
  - ↓ time-to-mental status resolution, and medical clearance
  - Low cost, adverse effect profile

Objectives

- IV levocarnitine vs. comparable historical controls
  - To compare time-to-medical clearance
  - To compare time-to-mental status resolution

- Characterize hyperammonia tendencies
  - Time–to-peak levels
  - Correlation
    - VPA / NH₃ levels with mental status derangement
Study Design

• Observational retrospective case series review
  – All patients meeting criteria:
    • 2002 through 2009 (7 years)
    – Investigational Review Board approved
  
• Two groups:
  1. Patients who received IV levocarnitine for acute VPA toxicity
  2. Historical controls with monitored NH₃ levels

Florida Poison Center Network

• FPIC/USVI – Jacksonville
  – 63,547 calls / year
    • ~180 calls / day
  – 42 counties
  – 104 hospitals

• FPIC – Network
  – 193,910 calls / year
    • ~ 531 calls / day
  – ~ 250 hospitals
Methodology

<table>
<thead>
<tr>
<th>Inclusion</th>
<th>Exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Acute or acute-on-chronic ingestion of VPA</td>
<td>• &lt; 2 recorded VPA levels</td>
</tr>
<tr>
<td>• Patients with AMS</td>
<td>• &lt; 2 recorded NH$_3$ levels</td>
</tr>
<tr>
<td>• Confusion, lethargy, drowsiness, coma</td>
<td></td>
</tr>
<tr>
<td>• Peak VPA &gt; 100 mcg/ml</td>
<td></td>
</tr>
<tr>
<td>• Peak NH$_3$ &gt; 35 mcg/dl</td>
<td></td>
</tr>
</tbody>
</table>

VPA: valproic acid; AMS: Altered Mental Status

Statistical Methods

• Sample Size: 1° Outcomes
  – Power of 80%
  – Detection difference of 15% with a standard deviation of 20%
  – Anticipated effect size 0.7
  – Statistical significance: $\alpha<0.05$ (two tailed)
  – Requires $n=34$ patients in each group
### Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>IV LEVO (n=43)</th>
<th>Control (n=43)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>34.3</td>
<td>35.9</td>
<td>0.60</td>
</tr>
<tr>
<td>Men</td>
<td>67%</td>
<td>53%</td>
<td>0.05</td>
</tr>
<tr>
<td>Women</td>
<td>33%</td>
<td>47%</td>
<td>0.05</td>
</tr>
<tr>
<td>Suicidal Intent</td>
<td>93%</td>
<td>88%</td>
<td>0.46</td>
</tr>
</tbody>
</table>

*LEVO: levocarnitine*

### Baseline Characteristics

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<th>p value</th>
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</thead>
<tbody>
<tr>
<td><strong>Past Medical History</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seizures</td>
<td>12%</td>
<td>12%</td>
<td>1.0</td>
</tr>
<tr>
<td><strong>Bipolar</strong></td>
<td>62%</td>
<td>67%</td>
<td>0.65</td>
</tr>
<tr>
<td>Unknown</td>
<td>26%</td>
<td>21%</td>
<td>0.61</td>
</tr>
<tr>
<td><strong>Multiple Drug Exposures</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CNS Depressants</td>
<td>65%</td>
<td>61%</td>
<td>0.65</td>
</tr>
<tr>
<td>Other</td>
<td>7%</td>
<td>9%</td>
<td>0.69</td>
</tr>
<tr>
<td>None Reported</td>
<td>28%</td>
<td>30%</td>
<td>0.81</td>
</tr>
</tbody>
</table>

*LEVO: levocarnitine; CNS: Central Nervous System*
### Baseline Characteristics

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<th>IV LEVO (n=43)</th>
<th>Control (n=43)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adjunct Therapies</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiple A/C</td>
<td>42%</td>
<td>30%</td>
<td>0.26</td>
</tr>
<tr>
<td>Lactulose</td>
<td>25%</td>
<td>24%</td>
<td>1.0</td>
</tr>
<tr>
<td>Lavage</td>
<td>3%</td>
<td>2%</td>
<td>1.0</td>
</tr>
<tr>
<td>Hemodialysis</td>
<td>16%</td>
<td>2%</td>
<td>0.058</td>
</tr>
<tr>
<td>None</td>
<td>40%</td>
<td>28%</td>
<td>0.25</td>
</tr>
</tbody>
</table>

LEVO: levocarnitine; CNS: Central Nervous System; A/C: Activated Charcoal

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<thead>
<tr>
<th>Characteristics</th>
<th>IV LEVO (n=43)</th>
<th>Control (n=43)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>VPA (mg/dl) Stratification</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>100 – 300</td>
<td>65%</td>
<td>60%</td>
<td>0.65</td>
</tr>
<tr>
<td>300 – 600</td>
<td>16%</td>
<td>28%</td>
<td>0.19</td>
</tr>
<tr>
<td>600 – 900</td>
<td>10%</td>
<td>10%</td>
<td>1.0</td>
</tr>
<tr>
<td>&gt; 900</td>
<td>10%</td>
<td>2%</td>
<td>0.36</td>
</tr>
<tr>
<td><strong>NH₃ (mcg/dl) Stratification</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 - 80</td>
<td>21%</td>
<td>51%</td>
<td>0.004</td>
</tr>
<tr>
<td>80 - &gt;300</td>
<td>79%</td>
<td>49%</td>
<td>0.004</td>
</tr>
</tbody>
</table>

LEVO: levocarnitine
### Primary Outcome
#### Time-to-Medical Clearance

<table>
<thead>
<tr>
<th></th>
<th>IV LEVO (n=43)</th>
<th>Control (n=43)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>4 days 17 hrs</td>
<td>3 days 20 hrs</td>
</tr>
<tr>
<td>Standard deviation</td>
<td>± 2 d 16 hrs</td>
<td>± 4 d 7 hrs</td>
</tr>
<tr>
<td>95% CI</td>
<td>3 d – 5.8 d</td>
<td>1.3 d – 7.4 d</td>
</tr>
<tr>
<td>Median</td>
<td>3 days 12 hrs</td>
<td>2 days 13 hrs</td>
</tr>
<tr>
<td>Median Difference</td>
<td>1 day 1 hrs</td>
<td></td>
</tr>
</tbody>
</table>

LEVO: Levocarnitine

**p value: 0.287**

### Primary Outcome
#### Time-to-Mental Status Resolution

<table>
<thead>
<tr>
<th></th>
<th>IV LEVO (n=43)</th>
<th>Control (n=43)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>2 days 23 hrs</td>
<td>2 days 3 hr</td>
</tr>
<tr>
<td>Standard deviation</td>
<td>± 2 days 6 hrs</td>
<td>± 3 days 20 hrs</td>
</tr>
<tr>
<td>95% CI</td>
<td>2d 5 hrs – 3d 17 hrs</td>
<td>22 hrs – 3d 8 hrs</td>
</tr>
<tr>
<td>Median</td>
<td>1 days 21 hrs</td>
<td>1 day</td>
</tr>
<tr>
<td>Median Difference</td>
<td>21 hrs</td>
<td></td>
</tr>
</tbody>
</table>

LEVO: Levocarnitine

**p value: 0.108**
Secondary Outcomes
Characterization of Hyperammonia Levels

<table>
<thead>
<tr>
<th>Time</th>
<th>VPA Levels</th>
<th>NH₃ Levels</th>
<th>L-Carnitine Initiated</th>
<th>Mental Status</th>
<th>Time of Ingestion</th>
<th>Medical Clearance</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 hrs</td>
<td>246</td>
<td>76</td>
<td>1d 7 hrs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24 hrs</td>
<td>102</td>
<td>41</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>36 hrs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3d 5 hrs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Secondary Outcome
Time-to-Peak Ammonia Levels

<table>
<thead>
<tr>
<th></th>
<th>IV LEVO (n=43)</th>
<th>Control (n=43)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>1 day 4 hrs</td>
<td>1 day 4 hrs</td>
</tr>
<tr>
<td>Median</td>
<td>24 hrs</td>
<td>23 hrs</td>
</tr>
<tr>
<td>95% CI</td>
<td>23 hrs – 1 d 10 hrs</td>
<td>23 hrs – 1 d 10 hrs</td>
</tr>
<tr>
<td>Median Difference</td>
<td>9 min</td>
<td></td>
</tr>
</tbody>
</table>

LEVO: Levocarnitine

p value: 0.9346
Results
Pearson Product of Correlation

• ↑ VPA : ↑ NH₃
  – r = 0.38
  – r² = 14%

• ↑ NH₃ : ↓ Mental Status
  – r = 0.02
  – r² = 0.04%

• ↑ VPA : ↓ Mental Status
  – r = 0.15
  – r² = 2.3%

Post-Hoc Survey Question

• Population: Toxicologists of American Poison Centers
  • n = 140
  • Response: n = 48 (34.3%)
Limitations

- Comparison of historical controls
- Identified confounders
- Reporting bias
- Recording bias
  - Time of reported ingestion
  - Time levels drawn for VPA and ammonia
  - Time of mental status change initiation and resolution
- Determination of IV levocarnitine dosing inconsistent or unknown

Discussion

- Platform for future evidence based studies
- Levocarnitine place in therapy
  - Timing
  - Dosing
  - Risk stratification
    - Chronic vs. Acute
- Hyperammonemia characterization
  - Following NH₃ levels
  - Risk stratification
Clinical Benefit?

- Speed the decrease of ammonia in patients with VPA induced encephalopathy
- Correlation of NH₃ and clinical condition is unfounded
- Hastening the recovery from unconsciousness has not been clearly established
  - Metabolic pathways have been shown to normalize

Summary

- Benefit of L-carnitine on clinical outcome has not been demonstrated
- Lack of significant adverse effects
- Affordable cost
- IV levocarnitine
  - [VPA] > 450 mg/L
  - 100 mg/kg IV loading, then 50 mg/kg every 8 hours

Ann of Pharmacother 2010;44:1287-1293
Audience Assessment Question

Which of the following agents has been suggested to correct the underlying cause of hyperammonemia in acute VPA toxicity?

A. Lactulose
B. Levocarnitine (Carnitor®)
C. Rifaximin (Xifaxan®)
D. Hemodialysis
E. Multidosed activated charcoal

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Audience Assessment Question

Which of the following is a contraindication for the use of levocarnitine?

A. Glucose-6-phosphate dehydrogenase (G6PD) deficiency
B. Renal Insufficiency
C. No known contraindications
D. Coagulopathy
E. Methemoglobin reductase deficiency
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