Valproate overdose: what is the role of carnitine?

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Contents

• Role of L-carnitine in valproate metabolism
• Metabolic effects of valproate overdose
• Evidence for L-carnitine for valproate overdose
• L-carnitine pharmacokinetics and dosing
Carnitine

- Water-soluble amino acid derivative
- Diet (75%)
- Endogenous synthesis in liver and kidneys (L-carnitine only)
- Healthy adults: plasma L-carnitine 40-60 uM/L
- L-carnitine has 2 metabolic functions:
  - Role in fatty acid metabolism
  - Role in mitochondrial energy production
Valproate and valproic acid

- Simple branched chain carboxylic acid
VPA metabolism

Fig. 2. Liver metabolism of valproic acid.

Lheureux et al, 2009
Valproate β-oxidation –
the “carnitine shuttle”

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

- Valproylcarnitine excretion in urine
- Inhibited renal re-uptake of carnitine
- Endogenous carnitine synthesis inhibited
- Carnitine cellular uptake inhibited
- VPA metabolites bind to CoA, carnitine not released back to free stores

Lheureux et al, 2009
Pathogenesis of hyperammonaemia

↓ B-oxidation

2-en-VPA

↑ w-oxidation

4-en-VPA
Metabolic effects of valproate overdose

- Increased $\omega$-oxidation
- Reduced $\beta$-oxidation
- Build up of acyl groups
- Carnitine deficiency
- Hyperammonaemia
- Detection of 4-en-VPA
- Reduction in 2-en-VPA
- Reduced free carnitine and increased ratio of acylcarnitine : free carnitine
- Elevated Ammonia
Evidence of carnitine deficiency in acute VPA overdose

- 6 severe acute VPA toxicity cases
- Mean VPA 1127mg/L
- 5 ventilated, 4 dialysed, 2 deaths [cerebral oedema]
- All elevated ammonia
- All elevated acylcarnitine

- Eyer at al 2005
Evidence for carnitine as therapy in acute VPA overdose

<table>
<thead>
<tr>
<th>Reference</th>
<th>Pt. Age (y), Sex, Weight (kg)</th>
<th>Valproic Acid Ingested, g (mg/kg)</th>
<th>Coingestant</th>
<th>Initial Valproic Acid Concentration, mg/L (time since ingestion, h)</th>
<th>Peak Ammonia Level, μmol/L (time from admission, h)</th>
<th>GCS: On Admission, at Worst (time from admission, h)</th>
<th>L-Carnitine Dose</th>
<th>Other Care</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ishikura (1996)</td>
<td>16 mo, M, 9.7</td>
<td>4 (412)</td>
<td>None</td>
<td>1316 (3)</td>
<td>NR</td>
<td>Deep coma on admission, NR</td>
<td>100 mg/kg initially, then 250 mg q8h for 4 days; route not specified</td>
<td>Gastric lavage, activated charcoal, intravenous fluids, urinary alkalization</td>
<td>Recovered LOC on day 4, discharged home on day 8 without sequelae</td>
</tr>
<tr>
<td>Murakami (1996)</td>
<td>15 mo, M, 10</td>
<td>4 (400)</td>
<td>None</td>
<td>1316 (2)</td>
<td>49 on admission</td>
<td>NR, NR</td>
<td>100 mg/kg NG daily for 3 days</td>
<td>Gastric lavage, intravenous fluids</td>
<td>Recovered LOC on day 3, discharged home on day 8 without sequelae</td>
</tr>
<tr>
<td>Houghton (2003)</td>
<td>29, F, NR</td>
<td>NR</td>
<td>Acetaminophen, propoxyphene, diphenhydramine, diazepam, ethanol</td>
<td>337(2)</td>
<td>200 at admission</td>
<td>11, 3 (–8)</td>
<td>100 mg/kg NG daily</td>
<td>Activated charcoal, naloxone, N-acetylcysteine, supportive measures</td>
<td>Recovered LOC on day 3, discharged to psychiatric care on day 6 without sequelae</td>
</tr>
<tr>
<td>Minville (2004)</td>
<td>36, M, NR</td>
<td>&gt;60</td>
<td>None</td>
<td>560 (NR)</td>
<td>NR</td>
<td>7, NR</td>
<td>50 mg/kg daily for 4 days; route NR</td>
<td>Gastric lavage, hemodialysis</td>
<td>Recovered; discharged from intensive care at 48 h; admitted to psychiatric care</td>
</tr>
<tr>
<td>Chan (2007)</td>
<td>Case 1: 14, F, 50</td>
<td>20 (400)</td>
<td>None</td>
<td>288 (10)</td>
<td>74 at admission</td>
<td>15, 14 (18)</td>
<td>3 g IV for 3 doses over 24 h</td>
<td>NR</td>
<td>Recovered LOC at 30 h post-ingestion; discharged home on day 2 without sequelae</td>
</tr>
<tr>
<td></td>
<td>Case 2: 19, M, NR</td>
<td>NR</td>
<td>None</td>
<td>950 (unknown)</td>
<td>65 (28)</td>
<td>10, NR</td>
<td>3 g IV q8h for 4 days</td>
<td>Activated charcoal, supportive measures</td>
<td>Recovered LOC at day 2; discharged home on day 7 without sequelae</td>
</tr>
<tr>
<td>Sikma (2008)</td>
<td>41, M, NR</td>
<td>100</td>
<td>None</td>
<td>1308 (&gt;10)</td>
<td>NR</td>
<td>3, 3 (0)</td>
<td>NR</td>
<td>Intravenous fluids, activated charcoal</td>
<td>Recovered LOC at 36 h from admission, discharged home on day 17 without sequelae</td>
</tr>
<tr>
<td>Jung (2008)</td>
<td>23, F, NR</td>
<td>24</td>
<td>None</td>
<td>1159 (4)</td>
<td>226 (day 2)</td>
<td>3, 3 (0)</td>
<td>20 mg/kg IV q8h for 2 days, then 200 mg/kg IV q8h for 3 days, then 100 mg/kg IV q8h for 1 day</td>
<td>Activated charcoal, activated charcoal hemoperfusion, lactulose</td>
<td>Improved by day 16</td>
</tr>
</tbody>
</table>

GCS = Glasgow Coma Scale; LOC = level of consciousness; NG = nasogastric; NR = not reported.
Carnitine- metabolic effects?

Ishikura et al.
- 16 month old 9.7 kg
- 4g VPA (412 mg/kg)
- VPA 1316 mg/L
- Deep coma
- Low β-oxidation and increased ω-oxidation metabolites
- 4-en-VPA increased
- L-carnitine for 4 days
- No haemodialysis
- Recovered LOC on day 4

Murakami et al.
- 15 month old 10 kg
- 4 g VPA (400 mg/kg)
- VPA 1316 mg/L
- Deep coma
- Low β-oxidation and increased ω-oxidation metabolites
- 4-en-VPA increased
- L-carnitine for 3 days
- No haemodialysis
- Recovered LOC on day 3
Carnitine- effect on GCS?

Sikma et al.
• 41 yr old
• 100g VPA
• Comatose on admission
• VPA 1308 mg/L (>10h)
• Ammonia 123 umol/L
• AC every 3 h
• L-carnitine (dose not given)
• VPA (961 → 622 → 204 → 79 at 0, 23, 36 and 55h from admission)
• Awoke at 36h

Chan et al. Case 2
• 19 yr old
• Unknown dose
• GCS 10/15 on admission
• VPA 950 mg/L (1h)
• Ammonia 43 umol/L
• AC 50g every 4h
• L-carnitine (3g iv 8hrly for 3 days)
• VPA (950 → 450 → 384 → 78 at 1, 8, 11 and 28h from admission)
• GCS 15 at 34h
Carnitine – effect on ammonia?

Jung et al.

- 23 yr old
- 24g VPA
- GCS 3
- VPA 1150 mg/L
- Ammonia 129
- 2h: AC haemoperfusion x 6h → VPA 629
- Day 2: AC HP → VPA 278
- Day 3: AC HP → VPA 40

- Day 2: Ammonia 317
  - L-carnitine 60mg/kg iv in 3 doses
- Day 3: L-carnitine 600mg/kg/day iv
- Day 4: Ammonia 60
  - L-carnitine 300mg/kg/day iv in 3 doses
  - Patient alert
  - Ammonia normalised
Carnitine safety

• LoVecchio, 2004
  – US Poisons centre charts: 674 acute VPA overdoses
  – 251 L-carnitine doses administered
  – Route unspecified
  – No allergic or hypotensive reactions
L-carnitine dosing?

• Formulations in UK: tablets, oral solution, iv
• Indications:
  – Primary deficiency
    PO 200mg/kg daily max 3g in 2-4 divided doses
    IV max 100mg/kg in 2-4 divided doses
  – Secondary deficiency
    20 mg/kg IV after each dialysis session
Oral L-Carnitine

- Absolute oral bioavailability 15%
  - Similar with both tablets and oral solution

- 2g vs 6g single oral doses in 6 healthy volunteers (Harper et al 1988)
  - Oral: saturable absorption (bioavailability 16% - 2g vs 5% - 6g)

- Oral L-carnitine 0, 0.5, 1, and 2 g 3 times a day for 7 days in 7 healthy volunteers (Bain et al 2006)
  - Plasma L-carnitine concentrations
  - Increased renal clearance at higher doses

<table>
<thead>
<tr>
<th>Parameter and unit</th>
<th>Oral solution</th>
<th>Tablet</th>
<th>Chewable tablet</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC (µmol • h/L)</td>
<td>779.9</td>
<td>771.4</td>
<td>762.6</td>
</tr>
<tr>
<td>Cₘₐₓ (µmol/L)</td>
<td>80.3</td>
<td>79.2</td>
<td>76.8</td>
</tr>
<tr>
<td>Cₘᵢₙ (µmol/L)</td>
<td>54.2</td>
<td>54.5</td>
<td>53.8</td>
</tr>
<tr>
<td>tₘₐₓ (h)</td>
<td>3.3</td>
<td>3.4</td>
<td>3.1</td>
</tr>
</tbody>
</table>

AUC = area under the concentration-time curve; Cₘₐₓ = peak plasma concentration; Cₘᵢₙ = trough plasma concentration; tₘₐₓ = time to Cₘₐₓ.
Intravenous L-carnitine

- Initial volume of distribution 0.2-0.3 L/kg
- Initial t1/2 0.5-1h, terminal t1/2 3-12h
- Concentration back to baseline after 12-24 h
- Threshold for tubular reabsorption 40-60 uM/L
- IV: dose-related elimination due to saturable tubular reabsorption (renal clearance 78 mL/min after 2g dose and 100 mL/min after 6 g IV dose) Harper et al
- Suggested bolus dosing: 40-60 X 0.2-0.3 = 8-18 uM/kg = 1.5 – 3 mg/kg
- Extraction ratio during haemodialysis 0.70 (Evans et al 2000)
Conclusions

• Biological plausibility for use of L-carnitine
• Limited evidence of improved outcome
• Well-tolerated, few adverse effects
• Haemodialysis effective in clearing VPA and its metabolites as well as ammonia.
• Indications for L-carnitine not well-defined but consider in patients with severe acute VPA overdose, when haemodialysis is not readily available
  – VPA concentrations > 850mg/L
  – hyperammonaemia
  – hepatotoxicity
• Dosing and duration of treatment unclear
  – Low bolus intravenous doses e.g 1.5 - 3 mg/kg 4-6hrly
Thank you for your attention

Gracias