L-CARNITINE

DEPARTMENT OF CLINICAL TOXICOLOGY
LOGHMAN POISON CENTER

Mitra Rahimi MD
- L-Carnitine (levocarnitine) is an amino acid that is vital to mitochondrial utilization of fatty acids.
INDICATIONS:

- FDA:
  Inborn errors of metabolism, hemodialysis, valproic acid toxicity, and for zidovudine (AZT)-induced mitochondrial myopathy & pediatric cardiomyopathy.
L-Carnitine decreases valproic acid-induced hyperammonemia and limits valproic acid-induced hepatic toxicity.
• L-Carnitine *should* be administered *IV* to symptomatic patients because of the limited bioavailability after oral (PO) administration.
HISTORY

- L-Carnitine is found in mammals, in many bacteria, and in very small amounts in most plants.
- "Carnitine was first discovered in 1905 in extracts of muscle, and its name is derived from *earn is, the Latin word* for flesh." Over the next 25 years, its chemical formula and structure were identified, and in 1997, its enantiomeric properties were confirmed.
- Carnitine was formerly known as vitamin BT.
Enzymes in the outer and inner mitochondrial membranes (carnitine palmitoyltransferase and carnitine acylcarnitine translocase) catalyze the synthesis, translocation, and regeneration of L-carnitine."
CHEMISTRY

- Fatty acids provide 9 kcal/g and are an important source of energy for the body, especially for the liver, heart, and skeletal muscle.
- The utilization of fatty acids as an energy source requires L-carnitine mediated passage through both the outer and inner mitochondrial membranes to reach the mitochondrial matrix where oxidation occurs.
Acyl-coenzyme A (CoA) is transported by carnitine from the cytosol to the mitochondria and undergoes p-oxidation in the mitochondrial matrix, generating acetyl-CoA, which then enters the citric acid cycle for the generation of ATP.
L-CARNITINE HOMEOSTASIS

- Approximately 54% to 87% of the body stores of L-carnitine is derived primarily from meat and dairy products in the diet; the remainder is synthesized.
PHARMACOKINETICS OF EXOGENOUS L-CARNITINE

- L-Carnitine is not bound to plasma proteins.
- Its Vd is 0.7 L/kg.
- Baseline serum concentrations for L-carnitine are 40 umol/L but increase to 1600 umol/L after administration of 40 mg/kg IV over 10 minutes. Whereas 2 g of L-carnitine administered IV produces a peak plasma concentration of 1000 umol/L,
- PO administration of 2 g produces peaks of only 15 to 70 umol/L.
Valproic acid and hyperammonemia

- Valproic acid may cause hyperammonemia (defined as serum ammonia concentration >80 ug/dl. or >35 umol/L) regardless of symptoms or liver function.
• Hyperammonemia and hepatic toxicity may be associated either with **therapeutic dosing** or an **acute overdose**.
• Valproic acid stimulates glutaminase, favoring glutamate uptake and ammonia release from the kidney.

• Reduced glutamate concentrations lead to impaired production of N-acetylglutamate (NAGA), a cofactor for carbamoyl phosphate synthetase I (CPS I), which is used in the liver to synthesize urea from ammonia.
Valproic acid therapy is commonly associated with a transient dose related asymptomatic increase in liver enzyme concentrations.

A rare symptomatic, life-threatening, idiosyncratic hepatotoxicity similar to Reye syndrome.
"RETROSPECTIVE ANALYSIS"

- When 50 patients with acute, symptomatic hepatic dysfunction who were not treated with L-carnitine were compared with 42 similar patients treated with L-carnitine, only 10% of the untreated patients survived but 48% of the L-carnitine-treated patients survived.
• Early diagnosis of patients, prompt discontinuance of valproic acid, and administration of IV rather than PO
• L-carnitine resulted in the greatest survival
• Most patients received 50 to 100 mg/kg/d of L-carnitine regardless of the route of administration."
L-CARNITINE CONCENTRATIONS

- In adults who eat all food groups and children older than 1 year of age, the normal serum concentrations of free L-carnitine are 22 to 66 umol/L and of total L-carnitine concentrations are 28 to 84 umol/L.

- Vegetarians have L-carnitine concentrations 12% to 30% lower than omnivores."
ADVERSE EFFECTS AND CONTRAINDICATIONS TO L-CARNITINE
- L-Carnitine administration is well tolerated."
- Transient nausea and vomiting are the most common side effects reported,
- with diarrhea and a fishy body odor
- noted at higher doses.'
• There are **no known contraindications** to the use of L-carnitine.

• L-carnitine is considered FDA pregnancy Category B.
**DOSAGE AND ADMINISTRATION**

- The **optimal** dosing of t-carnitine for valproic acid-induced hyperammonemia
- or hepatotoxicity has **not been established**.

Recommendations for IV L-carnitine administration to patients with acute metabolic disorders resulting from L-carnitine deficiency range from

- **50 to 500 mg/kg/d.**
AVAILABILITY

- sterile injection for IV use in 1 g/5 mL
- single-dose vials.
- L-Carnitine (Carnitor) is also available as a 330-mg tablet;
- As an PO solution with artificial cherry flavoring of 100 mg/ml.."
• A loading dose equal to the daily dose may be given initially, followed by the daily dose divided into every 4 hourly doses.
• We suggest a maximal daily dose of 6 g.
PO DOSING:

50 to 100 mg/kg d up to 3 grl d
and should be reserved for patients who are not acutely ill.
1) For patients with an *acute overdose* of valproic acid and without hepatic enzyme abnormalities or symptomatic hyperammonemia:

- L-carnitine administration can be considered prophylactic, and enteral

- doses of 100 mg/kg/d divided every 6 hours up to 3 g/d are appropriate.
2) For patients with valproic acid-induced **symptomatic hepatotoxicity** or **symptomatic hyperammoneremia**, 

- **IV L-carnitine:**

  - We suggest a dose of 100 mg/kg IV up to 6 g administered over 30 minutes as a loading dose followed by 15 mg/kg every 4 hours administered over 10 to 30 minutes.