TEXAS Health and Human Services

Levocarnitine (Carnitor®)

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Classification: Dietary supplement

Pharmacology:

- Mechanism of action: Carnitine is a naturally occurring metabolic compound which functions as a carrier molecule for long-chain fatty acids within the mitochondria, facilitating energy production. Carnitine deficiency is associated with accumulation of excess acyl CoA esters and disruption of intermediary metabolism, which may lead to a buildup of excess organic or fatty acids in patients with defects in fatty acid metabolism.[1,2]

Pharmacokinetics:

- Absorption: Following 4 days of dosing 1980 mg of Carnitor® tablets BID or 2 g of Carnitor® oral solution BID, the maximum plasma concentration was about 80 µmol/L and the time to maximum plasma concentration occurred at 3.3 hours. The absolute bioavailability of levocarnitine, calculated after correction for circulating endogenous plasma concentrations of levocarnitine, was 15.1 $\pm$ 5.3% for Carnitor® Tablets and 15.9 $\pm$ 4.9% for Carnitor® Oral Solution.[1]
- Distribution: V_d ~ 29 L (0.39 L/kg). The plasma concentration profiles of levocarnitine after a slow 3 minute intravenous bolus dose of 20 mg/kg of Carnitor® were described by a two-compartment model. Using plasma concentrations uncorrected for endogenous levocarnitine, the mean distribution half life was 0.585 hours.[1]
- Metabolism: In a pharmacokinetic study where five normal adult male volunteers received an oral dose of [^{3}H-methyl]-L-carnitine following 15 days of a high carnitine diet and additional carnitine supplement, 58 to 65% of the administered radioactive dose was recovered in the urine and feces in 5 to 11 days. Major metabolites found were trimethylamine N-oxide, primarily in urine (8% to 49% of the

administered dose) and [^{3}H]-γ-butyrobetaine, primarily in feces (0.44% to 45% of the administered dose).[1]

- Elimination: Following a single IV administration, approximately 76% of the levocarnitine dose was excreted in the urine during the 0-24h interval, 4% to 8% as unchanged drug. The mean apparent terminal elimination half life was 17.4 hours. Total body clearance of levocarnitine (Dose/AUC including endogenous baseline concentrations) was a mean of 4.00 L/h.[1]

Indications:

- Carnitine deficiency (primary or secondary)
- Carnitine deficiency in patients with ESRD requiring dialysis [injection only]
- Valproic acid induce hyperammonemia (off-label use)

Dosage:

- Carnitine deficiency (primary or secondary): Oral:
    - Tablet: Initial: 990 mg two to three times a day, depending on clinical response.
    - Oral solution: Initial: 1,000 mg/day in divided doses (every 3 to 4 hours); titrate slowly as needed up to 3,000 mg/day in divided doses based on tolerance and therapeutic response; higher doses may be needed in some patients (administer with caution).
- Carnitine deficiency (secondary): IV: 50 mg/kg/day in divided doses (every 3 to 4 hours, no less than every 6 hours). Doses may go up to 300 mg/kg/day (maximum reported). In patients with severe metabolic crisis, a 50 mg/kg loading dose followed by an additional 50 mg/kg over the next 24 hours in divided doses may be required.
- Valproic acid hyperammonemia,: 1980-2500mg divided twice daily per published case reports

Administration:

- Carnitor® Tablets and Carnitor® Oral Solution are for oral use only. Not for parenteral use.

Storage:

- Carnitor® Tablets and Carnitor® Oral Solution are stored at controlled room temperature (25°C).

Contraindications:

- No contraindications known according to the manufacturer's labeling.

Precautions:

- Gastrointestinal effects: Gastrointestinal reactions may occur from rapid consumption of oral carnitine; evenly space doses throughout the day and consume slowly to maximize tolerance.
- Hypersensitivity reactions: Serious hypersensitivity reactions have been reported after oral and IV administration. Reactions to oral levocarnitine include rash, urticaria, and facial edema. Reactions to IV administration were primarily seen in patients with ESRD and included anaphylaxis, laryngeal edema and bronchospasms. Levocarnitine should be discontinued if hypersensitivity suspected and medical attention should be sought.

Interactions:

- Warfarin: INR increase has been reported when levocarnitine is taken comncurrently with warfarin. Frequent INR monitoring advised upon initiation and dose adjustment of levocarnitine.
- There are no known CYP450 interactions.

Adverse Reactions:

- Mild gastrointestinal complaints have been reported during long-term use of levocarnitine, including nausea, vomiting, diarrhea, and abdominal cramps. Seizures have been reported in patients with or without pre-existing seizure history though an increase in seizure frequency and/or severity has been reported in patients with pre-existing seizure activity. Other known adverse effects include mild myasthenia in uremic patients and drug-related body odor. Decreasing the dosage often diminishes or eliminates body odor or gastrointestinal symptoms when present.

Use in Special Populations:

- Renal impairment: The safety and efficacy of oral levocarnitine has not been evaluated in patients with renal insufficiency. Long-term administration of oral levocarnitine in patients with severe renal insufficiency or ESRD on dialysis may result in accumulation of toxic metabolites.
- Hepatic impairment: no dose adjustment provided in manufacturer's labeling.
- Pregnancy: Pregnancy Category B: No adverse effects or evidence of impaired fertility or harm to fetus during animal studies. There are no adequate and well controlled studies in pregnant women.

- Lactation: Animal studies show increase in levocarnitine concentration in milk following its administration. There are no studies specifically looking at levocarnitine supplementation in nursing human mothers.

Cost Comparisons:

Name	Strength (mg)	Manufacturer	Unit Cost-per tablet ($)
Carnitor	330	SIG	0.983
Levocarnitine	330	AKR	0.779
Levocarnitine	500	N-B	0.309 (average)

Monitoring:

- Periodic blood chemistry (CMP and CBC)
- Vital signs
- Plasma carnitine concentrations
- Overall clinical condition

Efficacy:

- A retrospective cohort study evaluated the overall incidence and treatment management of VPA-induced hyperammonemia in 347 adult patients admitted to the psychiatric unit at a community teaching hospital.[3] The study's primary outcome was the prevalence of hyperammonemia in these patients. The secondary outcomes looked at the prevalence of symptomatic hyperammonemia and the prevalence and efficacy of treatments for hyperammonemia. The choices for treatment included discontinuation of VPA, VPA dose reduction, lactulose, levocarnitine, or a combination of lactulose and levocarnitine. The standard dosing for lactulose was 20 g to 30 g three to four times daily, and the standard dosing for levocarnitine was 300 mg three times daily. Treatment success was defined as achieving an ammonia level of less than 47 µmol/L at discharge (or the most recent ammonia level if one was not drawn on the day of discharge). Decreases between the initial and final ammonia levels were also calculated, as percentages of the initial level. All patients had received at least one dose of VPA or divalproex sodium during admission and had at least one ammonia level drawn during admission. Patients were excluded if they had a diagnosis of cirrhosis. Of the 347 patients screened for hyperammonemia, 125 patients had ammonia levels

considered to be above the upper limit of normal (47 µmol/L, according to hospital protocol), and 113 of these patients were analyzed for the secondary treatment outcome. Discontinuation of VPA was shown to be the most successful (18/32, 56.3%), with levocarnitine therapy being the next most successful (19/38, 50.0%). However, the differences in success rates were statistically insignificant between all treatments overall (P=0.30). VPA discontinuation showed a mean percentage ammonia decrease of 27.4% compared to 8.9% if not discontinued (P=0.07), while levocarnitine showed a mean percentage ammonia decrease of 12.3% compared to 14.8% with other treatments or no treatment (P=0.73). There was not a significant difference in ammonia-level changes between patients treated with levocarnitine and untreated patients (P=0.09).

- A case series and literature review looked at a total of nine cases (three from chart review, six from a literature search) that utilized levocarnitine in VPA-treated patients with psychiatric disorders that had developed hyperammonemia[4]. Case 1 involved a 65-year old male with bipolar I disorder that was admitted for an acute manic episode. After being titrated up to 3,000 mg/day of valproate and 6 mg/day of risperidone, he developed somnolence with garbled speech and altered mental status. Laboratory testing revealed a VPA of 68 µg/mL and an ammonia level of 56 µmol/L. Valproate was discontinued and symptoms resolved. The patient was later started on lithium 900 mg/day and valproate 1,000 mg/day, which was eventually increased to 1,500 mg/day in two divided doses. At the time of the valproate dose increase, the patient was initiated on levocarnitine 990 mg daily and eventually titrated to 990 mg twice daily. Upon recheck, valproate level was 50 µg/mL and ammonia was 23 µmol/L with no symptoms of encephalopathy. Valproate was continued outpatient, but levocarnitine was not renewed (reason unknown). The patient was admitted to the hospital for encephalopathy about 3 months later with an ammonia level of 66 µmol/L and a valproate level of 19 µg/mL (as it was held for somnolence). Valproate was discontinued and not restarted. Case 2 involved a 64-year old male with schizoaffective disorder, bipolar type, whose valproate dosing was at 2,750 mg/day with a valproate trough of 141 µg/mL. An ammonia level was drawn and was 63 µmol/L. One dose of levocarnitine 990 mg was given. Ten hours later, ammonia

was decreased to 44 µmol/L. The patient was discharged on levocarnitine 990 mg daily for two days, then 990 mg twice daily. Eventually, the patient was readmitted to the hospital with a valproate level of 70 µg/mL on divalproex ER 2,500 mg/day and an ammonia level of 75 µmol/L. After 9 days of witnessed adherence to levocarnitine 330 mg three times daily, ammonia level decreased to 29 µmol/L. The patient was discharged on levocarnitine 990 mg twice daily to be continued with divalproex. Case 3 involved a 53-year old male with bipolar I disorder in an acute manic episode. Patient was on 2,000 mg/day valproate and ammonia level peaked at 82 µmol/L with valproate at 104 µg/mL. Lactulose was started for hyperammonemia and given for three days. Two days after lactulose initiation, levocarnitine was also initiated at 1,000 mg daily for three days, then increased to twice daily, and eventually to 1,000 mg every morning and 1,500 mg every evening. Ammonia levels decreased to a range of 46 to 59, and the patient was discharged on valproate and levocarnitine. The patient was eventually readmitted with a valproate level of 115 µg/mL and an ammonia level of 74 µmol/L, which decreased to 30 µmol/L after levocarnitine supplementation.

- A case report followed a 51-year old woman who intentionally ingested a dose of about 60 grams of valproic acid[5]. She presented within 30 minutes of ingestion and her treatment included multiple doses of activated charcoal, levocarnitine and hemodialysis, and required ICU admission with intubation and other supportive measures. The patient was first managed in the ED with 50 g of activated charcoal. At one hour, her VPA level came back at 379.6 µg/mL, and multiple doses of activated charcoal were started at 0.5 g/kg every 4 hours. A loading dose of levocarnitine was also administered at this time (100 mg/kg IV), followed by a maintenance dose of 15 mg/kg every 4 hours. Her VPA level continued to rise until peaking at 905.1 µg/mL about 12 hours after presentation. Continuous renal replacement therapy (CRRT) was planned and started 25 hours after the initial presentation. Eight hours following CRRT, her VPA level was at 417 µg/mL. Hemodialysis was initiated at this point for 8 hours, and the level dropped further to 94 µg/mL. Her ammonia levels were elevated, peaking at 393 mmol/L, but improved with management.

Safety:

- A retrospective, systematic review evaluated the use of intravenous levocarnitine for VHE from retrospective trials and case reports between 1948 and May 2011.[6] There were no reported adverse events in any of the evaluated trials, or in any of the more current trials. An additional systematic review evaluated the incidence of levocarnitine-induced seizures in patients on valproic acid, and found no literature supporting the claim that levocarnitine supplementation may induce seizures in patients on valproic acid.[7] There have been no reports of toxicity from levocarnitine overdose. Levocarnitine is easily removed from plasma by dialysis. The oral LD_{50} of levocarnitine in mice is 19.2 g/kg. High dose levocarnitine may cause side effects such as diarrhea.

Conclusions:

- Data for the efficacy and safety of levocarnitine is minimal, being limited to observational trials and case reports. In the available literature, levocarnitine has been shown to effectively reverse carnitine deficiency, reduce elevated ammonia levels, and improve symptoms of valproate-induced hyperammonemic encephalopathy. Levocarnitine has shown comparable efficacy to lactulose for reducing ammonia levels in patients with VPA-induced hyperammonemia. In addition, levocarnitine has also been shown to be effective in the prevention of hyperammonemia while on chronic valproate therapy. The adverse effect profile of levocarnitine is minimal, with no reported adverse events occurring in any recent studies, including increased risk of seizures, which was cited on the package insert and drug databases without references. Even at the maximum daily oral dose of 3 g/day, levocarnitine is an inexpensive choice for treatment.

Recommendation:

- Levocarnitine is a cost-effective option for VPA-induced hyperammonemic encephalopathy and for hyperammonemia prevention with chronic valproate therapy. Recommended for formulary approval for both indications.

References:

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4. Brown LM, Cupples N, Moore TA. Levocarnitine for valproate-induced hyperammonemia in the psychiatric setting: A case series and literature review. Ment Health Clin [Internet]. 2018;8(3):148-54. DOI: 10.9740/mhc.2018.05.148.
5. Al Jawder S, Al Jishi E, Al-Otaibi S, Al-Shahrani MS. All guns blazing: management and survival of massive valproic acid overdose – case report and literature review. Open Access Emergency Medicine: OAEM. 2018;10:31-36. doi:10.2147/OAEM.S151095.
6. Mock CM, Schwetschenau KH. Levocarnitine for valproic-acid-induced hyperammonemic encephalopathy. Am J Health Syst Pharm 2012; 69:35.
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