CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-567

APPROVED DRAFT LABELING

BEDFORD LABORATORIES

LVO-P00D

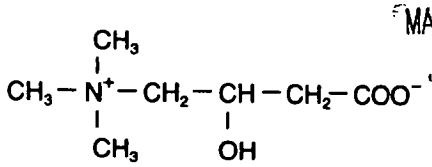
LEVOCARNITINE INJECTION USP

FOR INTRAVENOUS USE ONLY.

Rx ONLY.

DESCRIPTION

Levocarnitine is a carrier molecule in the transport of long chain fatty acids across the inner mitochondrial membrane. Levocarnitine Injection USP is a sterile aqueous solution containing 1 g of levocarnitine per 5 mL vial and 500 mg of levocarnitine per 2.5 mL vial. The pH is adjusted to 6.0 to 6.5 with hydrochloric acid. Chemically, levocarnitine is (R)-(3-Carboxy-2-hydroxypropyl)trimethylammonium hydroxide, inner salt. It is a white powder with a melting point of 196° to 197°C and is readily soluble in water, hot alcohol, and insoluble in acetone. The pH of a solution (1 in 20) is between 6 to 8 and its pKa value is 3.8. Its structural formula is:



Molecular Formula: $C_7H_{15}NO_3$ Molecular Weight: 161.20

CLINICAL PHARMACOLOGY

Levocarnitine is a naturally occurring substance required in mammalian energy metabolism. It has been shown to facilitate long-chain fatty acid entry into cellular mitochondria, thereby delivering substrate for oxidation and subsequent energy production. Fatty acids are utilized as an energy substrate in all tissues except the brain. In skeletal and cardiac muscle, fatty acids are the main substrate for energy production.

Primary systemic carnitine deficiency is characterized by low concentrations of levocarnitine in plasma, RBC, and/or tissues. It has not been possible to determine which symptoms are due to carnitine deficiency and which are due to the underlying organic acidemia, as symptoms of both abnormalities may be expected to improve with carnitine. The literature reports that carnitine can promote the excretion of excess organic or fatty acids in patients with defects in fatty acid metabolism and/or specific organic acidopathies that bioaccumulate acyl CoA esters.[1-6]

Secondary levocarnitine deficiency can be a consequence of inborn errors of metabolism or iatrogenic factors such as hemodialysis. Levocarnitine may alleviate the metabolic abnormalities of patients with inborn errors that result in accumulation of toxic organic acids. Conditions for which this effect was demonstrated are: glutaric aciduria II, methyl malonic aciduria, propionic acidemia, and medium chain fatty acyl CoA dehydrogenase deficiency.[7,8] Autointoxication occurs in these patients due to the accumulations of acyl CoA compounds that disrupt intermediary metabolism. The subsequent hydrolysis of the acyl CoA compound to its free acid results in acidosis that can be life threatening. Levocarnitine clears the acyl CoA compound by formation of acyl carnitine which is quickly excreted. Levocarnitine deficiency is defined biochemically as abnormally low plasma levels of free carnitine, less than 20 micromole/L at one week post term and may be associated with low tissue and/or urine concentrations. Further, this condition may be associated with a plasma concentration ratio of acylcarnitine/levocarnitine greater than 0.4 or abnormally elevated concentrations of acylcarnitine in the urine. In premature infants and newborns, secondary deficiency is defined as plasma free levocarnitine levels below age related normal levels.

Pharmacokinetics

In a relative bioavailability study in 15 healthy adult male volunteers Levocarnitine Tablets were found to be bio-equivalent to Levocarnitine Oral Solution. Following 4 days of dosing with 6 tablets of levocarnitine 330 mg bid or 2 g of levocarnitine oral solution bid, the maximum plasma concentration (C_{max}) was about 80 micromole/L and the time to maximum plasma concentration (T_{max}) occurred at 3.3 hours.

The plasma concentration profiles of levocarnitine after a slow 3 minute intravenous bolus dose of 20 mg/kg of levocarnitine were described by a two-compartment model. Following a single IV administration, approximately 76% of the levocarnitine dose was excreted in urine during the 0 to 24h interval. Using plasma concentrations uncorrected for endogenous levocarnitine, the mean distribution half-life was 0.585 hours and the mean apparent terminal elimination half-life was 17.4 hours.

The absolute bioavailability of levocarnitine from the two oral formulations of levocarnitine, calculated after correction for circulating endogenous plasma concentrations of levocarnitine, was 15.1 ± 5.3% for levocarnitine tablets and 15.9 ± 4.9% for levocarnitine oral solution.

Total body clearance of levocarnitine (Dose/AUC including endogenous baseline concentrations) was a mean of 4.00 L/h.

Levocarnitine was not bound to plasma protein or albumin when tested at any concentration or with any species including the human.[9]

Metabolism and Excretion

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. Maximum concentration of [^{3}H-methyl]-L-carnitine in serum occurred from 2 to 4.5 hr after drug administration. 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). Urinary excretion of levocarnitine was about 4 to 8% of the dose. Fecal excretion of total carnitine was less than 1% of the administered dose.[10]

After attainment of steady state following 4 days of oral administration of levocarnitine tablets (1980 mg q 12h) or oral solution (2000 mg q 12h) to 15 healthy male volunteers, the mean urinary excretion of levocarnitine during a single dose interval (12h) was about 9% of the orally administered dose (uncorrected for endogenous urinary excretion).

INDICATIONS AND USAGE

For the acute and chronic treatment of patients with an inborn error of metabolism that results in secondary carnitine deficiency.

CONTRAINDICATIONS

None known.

WARNINGS

None.

PRECAUTIONS

Carcinogenesis, Mutagenesis, Impairment of Fertility

Mutagenicity tests performed in *Salmonella typhimurium, Saccharomyces cerevisiae,* and *Schizosaccharomyces pombe* indicate that levocarnitine is not mutagenic. No long-term animal studies have been performed to evaluate the carcinogenic potential of levocarnitine.

Pregnancy:Teratogenic Effects - Pregnancy Category B.

Reproductive studies have been performed in rats and rabbits at doses up to 3.8 times the human dose on the basis of surface area and have revealed no evidence of impaired fertility or harm to the fetus due to levocarnitine. There are, however, no adequate and well controlled studies in pregnant women.

Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers
Levocarnitine supplementation in nursing mothers has not been specifically studied.

Studies in dairy cows indicate that the concentration of levocarnitine in milk is increased following exogenous administration of levocarnitine. In nursing mothers receiving levocarnitine, any risks to the child of excess carnitine intake need to be weighed against the benefits of levocarnitine supplementation to the mother. Consideration may be given to discontinuation of nursing or of levocarnitine treatment.

Pediatric Use
See **DOSAGE AND ADMINISTRATION.**

ADVERSE REACTIONS

Transient nausea and vomiting have been observed. Less frequent adverse reactions are body odor, nausea, and gastritis. An incidence for these reactions is difficult to estimate due to the confounding effects of the underlying pathology.

Seizures have been reported to occur in patients with or without pre-existing seizure activity receiving either oral or intravenous levocarnitine. In patients with pre-existing seizure activity, an increase in seizure frequency and/or severity has been reported.

OVERDOSAGE

There have been no reports of toxicity from levocarnitine overdosage.

Metabolic Disorders
Levocarnitine is easily removed from plasma by dialysis. The intravenous LD_{50} of levocarnitine in rats is 5.4 g/kg and the oral LD_{50} of levocarnitine in mice is 19.2 g/kg. Large doses of levocarnitine may cause diarrhea.

DOSAGE AND ADMINISTRATION

Levocarnitine Injection is administered intravenously. The recommended dose is 50 mg/kg given as a slow 2 to 3 minute bolus injection or by infusion. Often a loading dose is given in patients with severe metabolic crisis followed by an equivalent dose over the following 24 hours. It should be administered q3h or q4h, and never less than q6h either by infusion or by intravenous injection. All subsequent daily doses are recommended to be in the range of 50 mg/kg or as therapy may require. The highest dose administered has been 300 mg/kg.

It is recommended that a plasma carnitine level be obtained prior to beginning this parenteral therapy. Weekly and monthly monitoring is recommended as well. This monitoring should include blood chemistries, vital signs, plasma carnitine concentrations (the plasma free carnitine level should be between 35 and 60 micromoles/liter) and overall clinical condition.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Compatibility and Stability
Levocarnitine Injection USP is compatible and stable when mixed in parenteral solutions of Sodium Chloride 0.9% or Lactated Ringer's in concentrations ranging from 250 mg/500 mL (0.5 mg/mL) to 4200 mg/500 mL (8.0 mg/mL) and stored at room temperature (25°C) for up to 24 hours in PVC plastic bags.

HOW SUPPLIED

Levocarnitine Injection USP, 200 mg per 1 mL, is available in 5 mL single dose vials packaged 10 vials per carton (**NDC 55390-136-05**) and in 2.5 mL single dose vials packaged 10 vials per carton (**NDC 55390-136-03**).

Store vials at room temperature 25°C (77°F). Retain vial in carton until time of use. **Protect from light.** Discard unused portion of an opened vial, as they contain no preservative.

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