Use of Carnitine in FOD’s

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Acknowledgements

- Sigma tau Pharmaceuticals for research grants and funding of the NDAs for Secondary carnitine deficiency
- Children’s Hospital Central California
- Employees of Metabolic Research and Analysis, Inc.
L-Carnitine

- Originally Discovered in 1908--Tenebrio Molitor -- Essential for life -- Vitamin B_T

- Chemical structure deduced in 1952

- Carnitine is an amino acid derivative synthesized from lysine and methionine.

- Stored primarily in muscle.

- Body uses as a transporter molecule to move fatty acids into and out of the mitochondria.
Carnitine Sources

• Dietary sources of carnitine (75% of requirements) are:
  – Red meat
  – Dairy products
  – Breast milk

• 25% biosynthesized in liver and kidney from methionine and lysine
CARNITINE BIOSYNTHESIS IN THE HUMAN

Lysine + Methionine = Carnitine

- Initial synthesis of carnitine occurs in all tissues and involves many steps
- Intermediate synthesis occurs in the intestine, skeletal muscle, cardiac muscle, liver, kidney, and brain
- The final step occurs in the liver, kidney, and brain
- Lysine must be lysed from protein before it can be methylated.
L-Carnitine

\[
\begin{align*}
\text{CH}_3 & - \text{N}^+ - \text{CH}_2 - \text{CH} - \text{CH}_2 - \text{COO}^- \\
\text{CH}_3 & \quad \text{CH}_3 \\
\text{CH}_3 & \quad \text{OH}
\end{align*}
\]
Why Is Carnitine Essential?

• Carnitine is a natural substance vital to energy metabolism. It is responsible for:
  
  – **Transporting** long-chain fatty acids across mitochondrial membrane for conversion into ATP
  – **Modulating** intramitochondrial CoA/acyl-CoA ratio
  – **Scavenging** for potentially toxic acyl compounds
Pharmacologic Use of Carnitine in Rx of IEMs

Acyl-CoA → Acyl-Carnitine

- Enable excretion of toxic metabolite as Acylcarnitines
- Restoration of free CoA
- Prevention of deficiency

blood

urine
Carnitine Controversies

- Who is carnitine deficient?
- What are the causes of deficiency?
- When should you suspect deficiency?
- Where is the scientific evidence for treatment?
- How do you treat deficiency and for how long?
- Why do you treat deficiency?
Who is Carnitine Deficient?

• Tissue carnitine values 2 S.D. below the mean
• Plasma carnitine level of 20 micromoles/L or less
• Plasma acyl/free carnitine level of 0.4 or greater

What are the Causes of Carnitine Deficiency?

- **Primary Deficiency**
  - Defective biosynthesis
  - Transporter deficiency

- **Secondary Deficiency**
  - Decreased dietary intake
  - Defective intestinal absorption
  - Renal tubular reabsorbtion defect (Fanconi syndrome)
  - Increased acylcarnitine excretion

• Increased loss of Acyl Carnitine
  – Inborn Errors of Metabolism
  – Pharmacologic (Valproate, Pivalate)
  – Diabetes
• Increased loss of Free Carnitine
  – Renal tubular loss (Fanconi Syndrome
  – Hemodialysis, peritoneal Dialysis
• Decreased Supply
  – Soy milk based formulas unsupplemented
  – TPN
  – Cofactor Deficiency (Iron, vitamin C)
  – Substrate Deficiency
Carnitine Treatment of IEM

- 7439 entries in PubMed for carnitine
- 1582 for carnitine deficiency
- 544 for carnitine treatment of metabolic diseases
  - 1965-8/2002
First 36 Cases of Carnitine Deficiency (1965-1987)

- Encephalopathy (77%)
- Progressive Muscle Weakness (77%)
- Lipid Excess in Muscle (100%)
- Cardiomyopathy (23%)
- Low Serum Carnitine (89%)
- Low Muscle Carnitine (100%)
Pharmacologic Use of Carnitine in Rx of IEMs

Acyl-CoA → Acyl-Carnitine

- Enable excretion of toxic metabolite as Acylcarnitines
- Restoration of free CoA
- Prevention of deficiency
Initial Patient Experience

- **1982- MMA mut0-neonatal onset**
  - Only treatment-dietary/supportive
  - Long term prognosis fatal
  - **1983/1984-Carnitine treatment**
## Carnitine Values

<table>
<thead>
<tr>
<th></th>
<th>Plasma Micromoles/L</th>
<th>Urine Micromoles/L</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total</strong></td>
<td>17.4 N(30-70)</td>
<td>53.1 N(300-360)</td>
</tr>
<tr>
<td><strong>Free</strong></td>
<td>7.9 N(25-65)</td>
<td>7.5 N(140-200)</td>
</tr>
<tr>
<td><strong>Ester</strong></td>
<td>9.5 N(0-10)</td>
<td>45.6 N(140-200)</td>
</tr>
</tbody>
</table>

Metabolic Analysis Laboratory

Austin Shug, PhD
NEUTROPHIL COUNT - R.H.

Carnitine Begun

Thousands

Date

12/82
5/83
9/83
10/83
2/84
7/84
Plasma Carnitine Deficiency
51 Cases

- Hypotonia/ gross motor delay (85%)
- Recurrent infections with metabolic decompensations (85%)
- Failure to thrive (75%)
- Mental retardation (40%)
- Cardiomyopathy (30%)
- Encephalopathy (5%)

FDA approval of Carnitine for IEM (1987-1992)

• 1985- oral carnitine approved by FDA for treatment of primary carnitine def.

• 1992-NDA for treatment for secondary carnitine deficiency due to IEM based on retrospective data
  • Limited to disorders where Acyl CoA metabolites accumulate
    – 26 patients with biochemical evidence of efficacy
    – 48 patients with clinical evidence of efficacy
    – 18 historical controls untreated with carnitine
Historical Cohort (18)

• Disorders
  – Propionic acidemia - 10
  – Methylmalonic acidemia - 5
  – Glutaric aciduria II - 3

• Treatment
  – dietary
  – cofactor
  – alkali
  – anticonvulsants
Historical Cohort (18)

• **Outcome**
  – 18/18 died of their disorder
    • 12 prior to age 2
    • 6 between ages 2 and 17 after a life of recurrent episodes of decompensation and debilitating illness
  – 8/18 experienced recurrent metabolic decompensations
  – 10/18 had seizures
  – 8/18 were mentally retarded
  – 9/18 had failure to thrive
Clinical Efficacy Cohort (48 Patients)

• Centers
  – Fresno CA 19
    • Susan Winter, MD
  – San Diego CA 11
    • William Nyhan, MD
  – Portland OR 3
    • Neil Buist, MD
    • Berkley Powell, MD
  – Durham, NC 15
    • Charles Roe, MD
    • Steve Kahler, MD
Clinical Efficacy Cohort (48 Patients)

- Disorders
  - Glutaric Aciduria II (including EMA)  12
  - Methylmalonic acidemia  11
  - MCAD  8
  - Propionic acidemia  6
  - Isovaleric acidemia  3
  - Betaketothiolase deficiency  3
  - Glutaric aciduria I  2
  - SCAD  1
  - Hydroxymethylglutaryl CoA lyase def  1
Clinical Efficacy Cohort (48 Patients)

- Plasma Carnitine Levels
  - 20/48 with Free carnitine level below 20 micromoles/L
    - 25.4 +/- 17.3 micromoles/L (mean +/- SD)
  - 25/48 with Acyl/free carnitine ratio greater than 0.4
    - 1.11 +/- 1.82 (mean +/- SD)
Clinical Efficacy Cohort (48 Patients)

- Hospitalization Frequency data on 15/48
  - 0.491 per month prior to carnitine treatment
  - 0.075 per month after carnitine treatment instituted

- Growth Data on 32/48
  - 14 with weight below the 5%ile (Failure to thrive)
  - 8/14 crossed above the 5%ile

- 2/48 died during treatment period (4.1%)
26 biochemical evidence cohort

• Centers
  – Duke University 12 patients
    • Dr. Stephen Kahler
    • Dr. Charles Roe
  – CHCC (Fresno) 11 patients
    • Dr. Susan Winter
  – UCSD 3 patients
    • Dr. William Nyhan
Biochemical Evidence Cohort (26)

- Propionic acidemia 4 patients
- Methylmalonic acidemia 3 patients
- Glutaric aciduria II 4 patients
- MCAD 3 patients
- Isovaleric acidemia 1 patient
Biochemical Evidence Cohort (26)

- 15/26 plasma free carnitine deficient (below 20 micromoles/L)
- 20/26 plasma acyl/free ratio greater than 0.4
- Hospitalization frequency dropped from .319 days per month to .047 days per month with carnitine treatment
Biochemical Evidence Cohort (26)

- Resolution of failure to thrive in 5/9 patients with treatment
- Increased excretion of disease specific acylcarnitine species in 12 patients (only 12 had data available)
- Lowering of toxic metabolite levels documented in 11/26 patients
Biochemical Evidence Cohort (26)

- **MCAD**
  - Restoration of ketosis with 100 mg/kg oral carnitine load

- **Glutaric Aciduria II (ETF)**
  - Increased urinary excretion of glutaric acid with carnitine treatment versus baseline

- **Isovaleric Aciemia**
  - Increased urinary excretion of isovaleryl carnitine with carnitine treatment versus baseline value
Biochemical Evidence Cohort (26)

• Urinary excretion of hippurate increased with carnitine therapy
  – Isovaleric aciduria
  – Propionic aciduria
  – Methylmalonic aciduria

• Increased hippurate excretion evidence of increased availability of Coenzyme A for synthesis from Benzoyl CoA and ammonia
<table>
<thead>
<tr>
<th>Carnitine Intake (mg/kg/day)</th>
<th>Oral</th>
<th>I.V.</th>
<th>Date</th>
<th>Plasma Carnitine (µmol/L)</th>
<th>Free</th>
<th>Ester</th>
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<td></td>
<td>400</td>
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<td>7.2</td>
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<td>170.0</td>
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<td>338.8</td>
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<tr>
<td></td>
<td>0</td>
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<td>6/30</td>
<td>91.9</td>
<td>94.6</td>
<td>666</td>
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<tr>
<td>Date</td>
<td>Oral</td>
<td>I.V.</td>
<td>Free</td>
<td>Ester*</td>
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<td>6/30</td>
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<tr>
<td>24-hr Urinary Carnitine (mg/kg/day)</td>
<td>400</td>
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<td>3,201</td>
<td>3,652</td>
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<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>260</td>
<td>2,941</td>
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</table>

Carnitine Intake (μmol/L) 3,201 260 2,941

Total 7,832 11,946 11,250 12,500 12,300

Urinary esters identified on each specimen as propionylcarnitine.
<table>
<thead>
<tr>
<th>Days Oral IV</th>
<th>Propionylcarnitine mg/kg/d</th>
<th>mg/kg/mg Creat</th>
<th>Methylmalonic Acid (micromol/mg Creat)</th>
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<tbody>
<tr>
<td>1</td>
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<tr>
<td>2</td>
<td>5</td>
<td>8.9</td>
<td>86.4</td>
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<tr>
<td>3</td>
<td>100</td>
<td>38.9</td>
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<td>4</td>
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<td>43.7</td>
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<td>6</td>
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<tr>
<td>7</td>
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<td>45.4</td>
<td>127.3</td>
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<td>8</td>
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<tr>
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<td></td>
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<tr>
<td>18</td>
<td>666</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Cardiomyopathy
Adverse Events (26 patient cohort)

- Vomiting - 9/26 (37%)
- Diarrhea - 6/26 (23%)
- Abdominal pain - 3/26 (12%)
- Fishy odor (TMA) - 3/26 (12%)
- Alopecia/rash - 1/26 (4%)

- Death in one patient with propionic acidemia
Treatment of Trimethylaminuria Secondary to Oral Carnitine Therapy

- 7% of patients in FDA safety trials.
- Due to carnitine conversion by bowel bacteria to trimethylamines
  FMO3 mutations are common
- Treatment with metranidazole in low doses rapidly resolves odor.
- Doses used are 125-250 mg. per day for 10 days with repeated courses as necessary.
Safety in Fatty Acid Oxidation Defects

- Levocarnitine is approved by the FDA for the treatment of FODs
- Levocarnitine safety has been questioned in treatment of LCHAD
- Levocarnitine safety has been questioned in treatment of idiopathic cardiomyopathy due to concerns that the etiology could be LCHAD
Topics of Discussion

- Theoretical concerns with LCHAD
- Therapeutic experiences
  - VLCHAD
  - Other FODs
  - Cardiomyopathy
Concerns with LCHAD

• In reperfusion after MI
  – Fatty acid oxidation occurs at expense of glucose oxidation with resulting decreased recovery of cardiac function
  – Long chain acyl carnitine derivatives arrhythmogenic

• Other Factors to Consider
  – Levocarnitine restores Acyl CoA/CoA ratio
  – Long chain acyl carnitine derivatives are found in bile
Experimental Studies with MI

- CEIDM trial-Levoarnitine improved end diastolic and systolic volume vs. placebo
  – Collona, P, Iliceto S

- Levocarnitine reduces myocardial ischemic damage by increasing glucose and decreasing palmitate oxidation
  – Lopaschuk, G
FDA Safety Studies

- Secondary Carnitine Deficiency due to IEM
  - GI upset and odor main complications
  - No deaths felt attributable to carnitine
  - No cardiac arrythmias reported
Clinical Experience with LCHAD

- Metabol-I inquiry regarding arrhythmias with LCHAD treatment with levocarnitine revealed no cases.
- Two reports of infants with fatal arrhythmias at time of carnitine infusion-infants very unstable prior to receiving L-carnitine.
- No literature reports of actual cases of LCHAD and arrhythmias due to levocarnitine.
- Ventricular arrhythmias are associated with LCHAD in newborns
  - Bonnet, D, et al (Saudebray JM)
  - Rinaldo, P, et al
FOD Parents Support Group Report

- Voluntary survey done via e-mail in April, 2001
- 15 patients data received with known FOD
  - 5 with LCHAD
  - 9 with MCAD
  - 1 with TFP
LCHAD Cases

• 3 cases being treated with levocarnitine
  – 13 y M-7 yrs Rx- no complications
  – 10 y M-8.5 years on levocarnitine-Muscle cramps led to stopping carnitjne from 10/99 to 10/00. Restart in 10/00 due to RP and no muscle cramps or complication
  – 8 y M-7.5 years on levocarnitine-Muscle cramping initially and some GI upset but no complications at present
LCHAD Cases

• 5 y F-Carnitine given for short periods 14 and 17 months with rapid decrease in muscle strength and improvement off of levocarnitine with no ill effects
• 8 y F-Carnitine Rx from 17 months-5 y with muscle pain improved off of levocarnitine

TFP Case

• 22 y F-15 ys on levocarnitine with no complications
Nine MCAD Cases

• 7 cases treated for more than one year
• Complications
  – Muscle Cramping/pain-1
  – Body Odor-4
  – GI upset-3
MCAD - Improvements

- Increased stamina-4
- Increased muscle strength-3
- More Alert-3
- Decreased Irritability-2
- Decreased hypoglycemic episodes-1
Pediatric Cardiomyopathy Retrospective Study

• 10 year retrospective chart review from 7 centers (Helton et. al.)
  – 221 patients
    • 76 treated with Levocarnitine
      – 29 metabolic diagnoses
        » 3 LCHAD
    • 145 controls
      – 15 metabolic diagnoses
        » 3 LCHAD
Results

- Improved survival in levocarnitine treated versus untreated (NS)
- Significant improvement in ejection fraction, clinical severity scores and clinical functioning in levocarnitine treated versus placebo group
- Improved survival for first 100 days in the levocarnitine treated versus untreated metabolic patients. Long term survival in both groups the same.
Conclusions

• Although theoretical concerns exist regarding levocarnitine induced arrhythmias in LCHAD, only two patients identified with fatal arrhythmias.
• Levocarnitine treatment of pediatric cardiomyopathy improved outcome
### HOW TO TREAT
FDA APPROVED DOSING OF CARNITINE

<table>
<thead>
<tr>
<th>Oral</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants and children</td>
<td>• 50–300 mg/kg/day in divided doses; can slowly increase to maximum 3 g/day</td>
</tr>
<tr>
<td>Adults</td>
<td>• 1–3 g/day</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Intravenous</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute</td>
<td>• Loading dose 50-300 mg/kg, immediate bolus, followed by 50-300 mg/kg/day by continuous infusion or IV injection q 3–4 hr, never more than q 6 hr</td>
</tr>
<tr>
<td>Chronic</td>
<td>• 50-300 mg/kg/day by continuous infusion or slow bolus</td>
</tr>
</tbody>
</table>
Why?
Purpose of carnitine Treatment

• To treat carnitine deficiency which is characterized by low serum and/or tissue carnitine levels
• To treat symptoms due to carnitine deficiency
• To prevent deficiency
• Pharmacologic removal of potentially toxic acyl CoA metabolites in IEM
• Restore Acyl CoA/Free CoA ratio within mitochondria towards Free CoA