Parenteral Nutrition

"Are There Problems with Current Doses of Micronutrients?"

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Professor of Pharmaceutical and Clinical Nutrition

New Zealand
A.S.P.E.N. Research Workshop:
Micronutrients in Parenteral Nutrition:
Too Little or Too Much? (RW1/RW2)

Friday January 30, 8:00am – 6:45pm
Saturday, January 31, 8:00am – 5:15pm
Room: (C) 208-209
“No you can’t be a Beatle with that tie”
Liverpool

- Prof Sherwood Jones
- Dr Mike Peaston

Whiston Hospital
Liverpool

“intravenous feeding is routinely instituted if either oral or tube feeding is contraindicated”

“The Practitioner 1966”
Early HPN Patient – Dr Stan Dudrick
1970s
All-In-One (AIO) PN Admixtures

1977
First UK HPN patient at St Marks London

50+ components into a single bag
"Do you want the regular I.V. or fat-free?"
'Fat Friends? Stable Relationships?'

"Let's face it - our relationship is doomed."
Thin Friends 1980

Fat Friends 2005
Support Group:

Patients On Intravenous and Naso Gastric Nutrition Therapy

‘Supporting all patients on enteral and parenteral nutrition’

Contact and mutual support for people receiving artificial nutrition in the community

www.pinnt.co.uk

email: pinnt@dial.pipex.com

Registered Charity 327878
Equipment issues ...
The ‘Champagne Effect’

Are we Flogging a Dead Horse?
Multilayer Bags
Oxygen Impermeable

Eliminate Air Bubbles
No Champagne Effect

Minimise Vitamin Degradation
Micronutrients

9 Trace Elements

13 Vitamins

Vit D

Vit C

Vit E

Biotin
# Vitamins in Parenteral Nutrition

## Daily vitamin intake: AMA/NAG recommendations

<table>
<thead>
<tr>
<th>Vitamin</th>
<th>RDA-FNB *</th>
<th>AMA/NAG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin A (IU)</td>
<td>4000 - 5000</td>
<td>3300</td>
</tr>
<tr>
<td>Vitamin D (IU)</td>
<td>400</td>
<td>200</td>
</tr>
<tr>
<td>Vitamin E (IU)</td>
<td>15</td>
<td>10</td>
</tr>
<tr>
<td>Vitamin K</td>
<td></td>
<td>2 to 4 mg*</td>
</tr>
<tr>
<td>Vitamin B1 (mg)</td>
<td>1.0 - 1.5</td>
<td>3</td>
</tr>
<tr>
<td>Vitamin B2 (mg)</td>
<td>1.1 - 1.8</td>
<td>3.6</td>
</tr>
<tr>
<td>Nicotinamide (mg)</td>
<td>12 - 20</td>
<td>40</td>
</tr>
<tr>
<td>Pantothenic acid (mg)</td>
<td>5 - 10</td>
<td>15</td>
</tr>
<tr>
<td>Vitamin B6 (mg)</td>
<td>1.6 - 2.00</td>
<td>4</td>
</tr>
<tr>
<td>Biotin (µg)</td>
<td>150 - 300</td>
<td>60</td>
</tr>
<tr>
<td>Folic acid (µg)</td>
<td>400</td>
<td>400</td>
</tr>
<tr>
<td>Vitamin B12 (µg)</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Vitamin C (mg)</td>
<td>60</td>
<td>100</td>
</tr>
</tbody>
</table>

* FNB – Food and Nutrition Board oral RDA

* weekly
Each vial contains:

- Retinol palmitate corresponding to retinol 3500 IU
- Cholecalciferol 220 IU
- DL α-tocopherol corresponding to α-tocopherol 10.200 mg 11.200 IU
- Ascorbic acid 125.000 mg
- Cocarboxylase tetrahydrate corresponding to thiamine 5.800 mg 3.510 mg
- Riboflavin dihydrated sodium phosphate corresponding to riboflavin 5.670 mg 4.140 mg
- Pyridoxine hydrochloride corresponding to pyridoxine 5.500 mg 4.530 mg
- Cyanocobalamin 0.006 mg
- Folic acid 0.414 mg
- Dexpantenol 16.150 mg
- Corresponding to pantothenic acid 17.250 mg
- D-Biotin 0.069 mg
- Nicotinamide 46.000 mg
- Glycine 250.000 mg
- Glycocholic acid 140.000 mg
- Soybean phosphatides 112.500 mg
- Sodium hydroxide, Hydrochloric acid qs pH 5.9
Not your ordinary nutrients!

- Vitamins are catalysts for metabolic processes driven by enzymes
- Many enzymes contain Trace Elements as key components
- Many micronutrients are powerful Antioxidants
- Micronutrients are critical and life-saving

“Micro in content: Mega in importance”
Micronutrient - Synergisms

ROOH, ROH  Tocopherol  Ascorbate  GSSG  NADPH
Free radicals

ROO⁻, RO⁻  Tocopherol  Dehydro-  GSH  NADP

Vit E  Gpx (Se)  Vit B₁₂

Free Radicals  Antioxidants  Energy
Too Little: problems of inadequate micronutrients

Impaired Function
• ↓ Wound Healing
• ↓ Immunity
• ↑ Free Radicals

↓ Antioxidant Activity
Too Little: problems of inadequate micronutrients

Clinical Deficiency
Scurvy, osteomalacia, retinal problems

Lips: Lips of a tramp with acute scurvy.

Eye: Patient with slight circumcorneal vascularisation.

C Deficiency: Epithelial changes: sore, swollen lips.

B Deficiency: Vascular changes: slight circumcorneal vascularisation (riboflavin deficiency).
Thiamine in PN

- $B_1$ participates as co-enzyme in oxidative decarboxylation reactions
- essential in PN for glucose metabolism
  - body stores very limited
  - paediatric fatalities due to thiamine deficiency
  - death due to lactic acidosis, subsequent heart failure
Water-soluble Vitamins

- B group, Biotin, C, K, Folic acid
- Not stored by the body
- Must be taken on a regular basis, just as in a regular oral diet
- Excess excreted in the urine ("renal threshold")
- If given too rapidly, renal threshold is exceeded and vitamins lost in urine
- Unstable in air and sunlight
Vitamins A, D, E

- Soluble in body fat
- Stored by the body
- Can overdose (hypervitaminosis A)
- Overdoses can be toxic
- Care with storage and administration
- Vitamin A lost on bag and set surfaces
- Losses if exposed to sunlight
Vitamin D: Optimal Concentrations

- 80 nmol/liter of 25(OH)D
- 3-100 ng/ml of 25(OH)D
- 400 IU/day (DeLuca ASPEN 2009)
- 1600-1800 IU/day (Jacobs 2009)
Time in sunshine to achieve dietary equivalent of 1000 IU of vitamin D per day (Jacobs 2009)

25% exposure  Webb et al. skin types (1-6):

<table>
<thead>
<tr>
<th>Date, Skin Type</th>
<th>Tucson: Full sunshine at noon</th>
<th>NYC: Full sunshine at noon</th>
<th>NYC: Partly cloudy at noon</th>
</tr>
</thead>
<tbody>
<tr>
<td>July 20</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin Type 2</td>
<td>7 minutes</td>
<td>7 minutes</td>
<td>11 minutes</td>
</tr>
<tr>
<td>Skin Type 5</td>
<td>15 minutes</td>
<td>17 minutes</td>
<td>25 minutes</td>
</tr>
<tr>
<td>January 20</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin Type 2</td>
<td>28 minutes</td>
<td>1 hour, 19 min</td>
<td>2 hours, 5 min</td>
</tr>
<tr>
<td>Skin Type 5</td>
<td>1 hour, 8 min</td>
<td>3 hours, 45 min</td>
<td>2 hours, 25 min</td>
</tr>
</tbody>
</table>

Skin type 2: Caucasian, blond or red hair, freckles, fair skin, blue or green eyes
Very sensitive to UV; usually burns easily; tans with difficulty, fair skin tone

Skin type 5: Middle Eastern, Latin, Light African American, Indian
Minimally sensitive to UV; rarely burns, tans easily, olive or dark skin tone
Trace Elements

- Mn, Zn, Cu, Fe, Se
- Co-enzymes, structural, metabolic
- Traces usually obtained from food
- HPNers rely almost entirely on PN regimen

"Perhaps we had better cut back on our trace minerals."
Too Little or Too Much

- **Diarrhoea**
  - Zinc↓ Copper↓
- **Cholestasis**
  - Manganese↑
- **Renal insufficiency**
  - Aluminium↑
- **Blood loss**
  - Iron↓

**Hair Loss**
Iron↓ Zinc↓ Selenium↑ Biotin↓
Manganese (Mn)

• role: Mn S.O.D., pyruvate carboxylase Antioxidant protection Energy metabolism No PN deficiency (unless induced)

• dosage Adults: [150-800 μg/d (3-15 μmol/d)] AMA
[275μg/d] AuSPEN 1999
60 - 100 μg/d ASPEN 2004

WARNING: brain accumulation - cholestasis

Recommend: 55μg/day (1 μmol/d) ESPEN 2006
Infants : 1 μg/kg/d -1.5 μg/kg/d (max 50μg/d)

Hardy, Manzanares, Menendez Nutrition 2009
Hardy ASPEN Workshop 2009
Manganese in Long Term HPN Patients (Case Reports)

- 25y male HPN 5yrs and 57y male HPN 10yrs
- MTE additive: Zn, Cu, Cr, Se, Mn (500mcg/day)
- Plasma Mn: 59.9 and 42.0 nmol/l (normal :5.5-18.2 nmol/l)
- MRI showed Mn deposition in globus pallidus
- 9 mo after withdrawal of Mn = MRI normal
  
  Stevens et al NCP 2008:23;197

- 54 Peds (760g- 65.2kg)
  
  Received 20mcg/kg Cu and 5mcg/kg Mn per day
  
  15 ↑Cu: 21↑Mn: 7↑Cu & Mn: 20 had cholestasis
  
  Determine Cu and Mn levels monthly
  
  Mcmillan et al NCP 2008:23;161
Hypermanganesemia

• Numerous incidents of PN-associated Mn toxicity and/or hypermanganesemia

• Over 50% of HPN patients may have elevated Mn levels leading to hypermanganesemia
  – Cerebral, hepatic complications

• No reports of Mn Deficiency

• Mn contamination in additives

• Post mortem data confirm accumulation of Mn (Howard and Shenkin 2007)
Selenium

“Incorporated into Selenoproteins (25+)

- Glutathione Peroxidase (GPx) contains 4 atoms of Selenium
- Important antioxidant - removes lipid peroxides
- Anti-inflammatory - down regulates NFkB
- Essential for Male Fertility (XY) and Reproduction
  - GPx protects developing sperm

Only trace element specified in Genetic Code
i.e. Selenocysteine (21st Amino Acid)

“The Se-XY Nutraceutical”
Factors affecting micro-nutrient stability in PN

- Amino Acid buffering
- Fat Emulsion source
- Electrolytes and Antioxidants
- Concentrations of nutrients and pH
- Sequence of Mixing

*Oxygen * Light * Heat

*Fig. 3. The degradation of ascorbic acid in TPN mixtures containing 10 ml M.Y.C. 9+3 Vitagard during storage at 5°C in EVA (squares) or Ultratab multilayer (circles) bags, with closed and without (open) fat emulsion.*

Allwood & Hardy Clin Nutr 1992
Trace Elements vs Vitamins in PN

- Vitamin C oxidation is catalysed by copper ions or selenite
- Vitamin C losses 48 hours after mixing
- Selenite interacts with Vitamin C at low pH
- Ferric iron may destabilise lipid-PN
- Additives must be kept apart until immediately before administration
- Adverse influences of air and light
  - Protect all PN from Light!
Dosage Recommendations

- **Zinc**: 1-3mg/d adults
  - 12mg/L g.i losses, diarrhea
- **Copper**: 0.3mg/d adults
  - 0.4-0.5mg/d diarrhea
  - 20mcg/kg/d peds
- **Chromium**: 10-15mcg/d adults
  - 0.14-0.2mcg/kg/d peds
- **Selenium**: 60-100mcg/d adults
  - 2-2.5mcg/kg/d peds
- **Iron**: 1mg/d adult males
  - 1.5mg/d adult females
  - 500mcg/d peds
- **Iodine**: 70-150mcg/d adults
  - 1mcg/kg/d peds

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Gastroenterology 2009
Dosage Recommendations

- Vitamin C: 100-200mg/d adults
  - 20-100mg/d peds
- Vitamin D: 30-100 ng/ml 25OH D
  - 400 IU/d
- Vitamin K: 150mcg/d adults
  - 2.5-5mg/week
  - 10mcg/d peds
- Choline: 1-2g/d adults
- Carnitine 2-5mg/d adults
  
  *Gastroenterology 2009*

- Biotin: 60-69mcg/d adults
  
  *Daniells & Hardy COCNMC 2010*

- Vitamin B₁₂: 6-50mcg/d adults
  
  *Manzanares & Hardy COCNMC 2010*
More is not always better!

Your tests indicate unusually high levels of copper, zinc, and nickel...
More is not always better!

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Daily Requirement</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chromium</td>
<td>&gt;3mg</td>
<td>↑ joint degeneration, immune problems</td>
</tr>
<tr>
<td>Copper</td>
<td>&gt; 5mg</td>
<td>↑ behavioural problems, infections, anemia</td>
</tr>
<tr>
<td>Iron</td>
<td></td>
<td>↑ vomiting, diarrhoea, hyperglycemia</td>
</tr>
<tr>
<td>Manganese</td>
<td></td>
<td>↑ neuro symptoms</td>
</tr>
<tr>
<td>Selenium</td>
<td>&gt; 750 mcg/d</td>
<td>↓ Deiodination, ↑ hair + nail discoloration</td>
</tr>
<tr>
<td>Zinc</td>
<td>&gt; 50 mcg/d</td>
<td>↓ immunity</td>
</tr>
<tr>
<td>Vitamin C</td>
<td>&gt; 1 g/d</td>
<td>↑ oxalosis, acute RF</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>&gt; 150 mg/d</td>
<td>↑ mortality</td>
</tr>
<tr>
<td>Some Tocopherols</td>
<td></td>
<td>↑ toxic (tocotrienols)</td>
</tr>
</tbody>
</table>
Conclusion

• Long Term HPNers may have increased micronutrient requirements.

• Micro supplements can:
  – improve antioxidant capacity
  – enhance the immune response
  – reduce infection rates

• CARE:
  – A Trace is Good. More is not always Better
  – Make All Additions Aseptically: Protect from Light
  – Monitor regularly

• RESEARCH
Micronutrients: Future Research

- Better data on deficiency syndromes
- Optimum requirements in IF
- Synergy between micronutrients
- Efficacy of supra-physiological doses
- Better Analytical methods
- Stability and compatibility issues

Do you have other problems/questions?
Thanks to PN-DU

A Troop of Pendoos

“OUR AIM IS TO PROVIDE SUPPORT AND INFORMATION TO CONSUMERS, CARERS, AND PROVIDERS OF PARENTERAL NUTRITION”

What is PN-DU?

- We are a support group that has been set up specifically by and for Parenteral Nutrition users and their families/care at home (HPN)

We want to encourage all Home Parenteral Nutrition consumers in Australia and New Zealand to join us and exchange your experiences, problems and achievements.

Together we can provide comfort, strength and reassurance to each other and together we can have a louder and more influential voice on the future development of HPN products, HPN therapy and Home Care Services.

Check out our website to join us and post questions or comments:
http://parenteral.nutrition.down.under.web.com

or you can email us at:
contactpndu@gmail.com

Connect up for support and information

contactpndu@gmail.com
THANK YOU!

Here’s to the Next 25 Years !!!