Parenteral Nutrition: The Role of the Pharmacist in the Era of 3-chamber Bags

Stefan Mühlebach
Parenteral Nutrition: The Role of the Pharmacist in the Era of 3-chamber Bags

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The Swiss Capital Berne
View from Swissmedic to the Alpes
The Berner Oberland after the heavy rainfalls last week (Fluids can harm!)
Content

- Parenteral Nutrition Characteristics
- NST: Pharmacist’s Role
- Delivery Systems and their limits
- Pharmacist’s Role in PN Safety
- Conclusions
Parenteral Nutrition (PN)

- Parenteral Nutrition
- Total

Gastrointestinal Failure
Gastrointestinal Dysfunction
Impaired Enteral Absorption

Digestion
Assimilation

(Total)

Parenteral Nutrition
(Partial)
PN: Substrate Admixing inside the Body (Multi-bottle System)
PN: Characteristics (2)

Components

- Triglycerides
  - LCT, MCT, Ω-3

- Glucose

- Amino acids
  - Gln……

- Electrolytes
  - Na, K, Ca, Mg, P, Cl

- Trace elements
  - Fe, Zn, Mn, Cu, Cr, Mo, Se, F, J

- Vitamins
  - A, B, C, D, E, K...

Complications (Safety)

- Errors
  - Dosing
  - Administration

- Metabolic
- Microbial
- Mechanical
- Economic

Parenteral Nutrition (PN)

- Effective when indicated
- Higher risk of complications
  - i.v. access
  - Correct dosing
  - Aseptic preparation (individualisation)
  - Stability: complex pharmaceutical interactions
  - Higher costs compared to EN
  - Patients partly highly fragile (neonates, critically ill)
  - Long-term treatment (HPN)
- Multi-professional approach (pharmacist)
Content

- Parenteral Nutrition Characteristics
- NST: Pharmacist’s Role
Clinical Nutrition: Multi-professional Process

Nutrition Support Team

Diagnosis
Nutritional state

Patient Evaluation
Malnutrition risk

Prescription
Enteral Parenteral

Admixing Administration
GMP Handling

Patient Outcome

Benefits from NST (Review): JPEN 2004;28(4):251
PN: Pharmaceutical Tasks

Selection and Documentation of Products

Acquisition and Delivery

- Purchase and/or preparation (!)
- Distribution

Drug use and administration

- Recommendations and guidelines (dosages, interactions, i.v. administration...)

Control and Review

- Product quality
- Handling (correctness, legality, CIRS, safety)
- Analysis of indications, outcome
- Cost

Stock management, Waste
Hospital Manufacture and Compounding
PN AIO: Admixing outside the Body

Components

- Glucose
- Amino acids (Gln...)
- Lipid (LCT, MCT, Ω-3)
- Electrolytes (Na, K, Ca, Mg, P, Cl)
- Trace elements (Fe, Zn, Mn, Cu, Cr, Mo, Se, F, J)
- Vitamins (A, B, C, D, E, K...)

PN: Pharmaceutical Support
Compounding / Admixing

Risk reduction (Safety ↑)

- **Mechanical**: Documented stability of the admixtures
- **Metabolic**: Appropriate nutrient administration (individualisation)
- **Infective**: Aseptic compounding (ready to use)
- **Economic**: Preparation cost, Utilisation review
- **Convenience**: AIO: ready to use; single container
Content

• Parenteral Nutrition Characteristics
• NST: Pharmacist’s Role
• Delivery Systems and their limits
Ready to use AIO Admixture: Safe Practices

Components
(> 50)

- Dextrose
  - Na, K, Ca, P
- Amino acids
  - Na, K, Mg
- Lipid
- Trace elements
- Vitamins

1. Dextrose
2. Amino acids
3. LCT (MCT) fat
4. Na
5. K
6. Ca
7. Mg
8. Phosphate
9. Fe, Zn, Mn, Cu, Cr, Mo, Se, F, I
(Vit. A, B, C, D, E, K...)

AIO admixture
Limited stability

Industrial Production?

Driscoll. JPEN 2003;27:433
Lipid Peroxidation in EVA-AIO Admixtures: Influence of Trace Elements (TE) and Storage Conditions

Peroxide values
[mmol peroxides/L]

- 20-30°C / daylight with TE
- 20-30°C / daylight
- 2-8°C / light-protected with TE
- 2-8°C / light-protected

Steger, Mühlebach JPEN 2000;24:37-41
Industrial AIO Premixes (Standards): The 3-Chamber Bag

Container polymer (Sterilisation)

Injection port

Breakable connection or seal

Infusion port

Glucose

Lipid

Amino acids

Cover wrap (Oxygen protection)

## Standardised PN in Hospitals

*Nutrition 2004;20:528-535*

### Switzerland
- 86% adult standard PN: (HP: 16% compounded)

### France
- 79% adult standard PN: (HP 18% compounded)

### Belgium
- 86% adult standard PN: (HP 56% compounded)

<table>
<thead>
<tr>
<th>Hosp Category</th>
<th>Switzerland</th>
<th></th>
<th>France</th>
<th></th>
<th>Belgium</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median</td>
<td>Min-Max</td>
<td>*Ratio</td>
<td>Median</td>
<td>Min-Max</td>
</tr>
<tr>
<td>Univ</td>
<td>6,983(4)</td>
<td>1,874-9,725</td>
<td>5.1</td>
<td>13,017(18)</td>
<td>2,419-39,500</td>
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<tr>
<td>Non-Univ</td>
<td>1,351 (12)</td>
<td>60-7,506</td>
<td>3.9</td>
<td>2,490 (19)</td>
<td>350-6,760</td>
</tr>
<tr>
<td>Regional</td>
<td>651</td>
<td>4-2,890</td>
<td>3.9</td>
<td>267 (5)</td>
<td>30-3,159</td>
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<tr>
<td>Private</td>
<td>2,357 (6)</td>
<td></td>
<td></td>
<td>2,357 (6)</td>
<td></td>
</tr>
</tbody>
</table>

*Ratio: no of PN bags per year/bed in 2000; Home PN proportion 5-7% (CH, B), 20% (F)
HPN: Need for Individualisation of PN

Duration of HPN
Number of Regimens [n]

Mean ± SD [month]: 52.6 ± 40.5

Regimens per patient: 7.5 ± 6.5

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PN: Pharmaceutical Tasks

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Stock management, Waste
Lipid Emulsion Destabilisation

Lecithin emulsifier
\[ \Omega: 0.2 - 0.4 \, \mu m \]

\[ MFT_{\text{max}}: \text{mean max droplet diameter} \]
Droplet Distribution of i.v. Lipid Emulsions

Normal Probability Curve

PFAT<sub>5</sub> Dose Increase over 24-hour Infusion in Rats (2.3 ml/hr)

Half-life of increase: 1.2 hours
Lipid Emulsion Stability: Influence of Lipids and Amino Acids

AIO PN: 5 g lipid/L; 6 g N/L; 144 g dextrose /L; pH 4.9-5.3
Na⁺,K⁺ (60 mM), P (19 mM), trace elements
Ca++ (7.5 mM), Mg++ (10 mM),

<table>
<thead>
<tr>
<th></th>
<th>MCT vs Lipovenös</th>
<th></th>
<th>Amino Acids</th>
<th>Lipids</th>
<th>Amino Acids X Lipids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hausmann-Amin</td>
<td>0.002</td>
<td>0.111</td>
<td>0.594</td>
<td></td>
<td></td>
</tr>
<tr>
<td>vs Vamin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vamin</td>
<td>0.786</td>
<td>0.241</td>
<td>0.026</td>
<td></td>
<td></td>
</tr>
<tr>
<td>vs Proteinsteril</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hausmann-Amin</td>
<td>0.011</td>
<td>0.934</td>
<td>0.005</td>
<td></td>
<td></td>
</tr>
<tr>
<td>vs Proteinsteril</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ANOVA of MFT_{max} with repeated measures and two group factors
Significance over time (10 days); (p-values)

Lipid Emulsion Stability ($MFT_{\text{max}}$) 
Influence of Amino acids

AIO-Stability using Intralipid® ($MFT_{\text{max}}$)

$\text{Ca}^{++} 7.5 \text{ mM; Mg}^{++} 10 \text{ mM}$

Clin Nutr 1993;12(S2):59
Bag Plastic Film layers: Physical Phenomena Occurring

### LB028  The effects of packaging containers and manufacturer on the large-diameter tail of the globule size distribution of lipid injectable emulsions - Part 2

D. F. Driscoll¹, A. Thomas², K. Kluetsch², B. R. Bistrian¹, J. Nehne²  
¹Medicine, Harvard Medical School, Boston, United States, ²Hospital Care, B. Braun, Melsungen, Germany

### PFAT5 Levels in Various Lipids

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>G-Lipids (n)</th>
<th>P-Lipids (n)</th>
<th>3C-P Lipids (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>0.046±0.004% (4)</td>
<td>0.120±0.023% (2)</td>
<td>0.159±0.015% (2)</td>
</tr>
<tr>
<td>B</td>
<td>0.028±0.011% (3)</td>
<td>Not Available</td>
<td>0.006±0.002% (2)</td>
</tr>
</tbody>
</table>
Medication Errors with Parenterals


Multiple Step Preparation / Admixing
(Ready to use)

Incompatibilities
Admixing incompatible drugs
Incompatibility: Calcium phosphate Precipitation

Ca\(^{2+}\) + H\(_3\)PO\(_4\) → Ca\((H_2PO_4)_2\) + CaHPO\(_4\)

Solubility (H\(_2\)O)

RDA iv [mmol/kg]

<table>
<thead>
<tr>
<th>Calcium</th>
<th>Phosphate</th>
<th>Vol [ml/kg]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonates</td>
<td>0.5 - 1.5</td>
<td>120</td>
</tr>
<tr>
<td>Adults</td>
<td>0.1 - 0.2</td>
<td>25 - 30</td>
</tr>
</tbody>
</table>

April 18, 1994: FDA-Alert

Avoidable Medication Error
Aim: Prevent / treat undernutrition to improve patient's outcome
Best use of clinical nutrition

Council of Europe (2002)
- Responsibility defined
- Education and training
- Patient-oriented
- Multidisciplinary nutrition support teams
- Implementation top down (Guidelines and recommendations)

Akt Ernähr Med 2003;28:133-136
PN: Pharmaceutical Tasks

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Stock management, Waste
Drug admixing in PN: Pharmaceutical Aspects

Adapted from „Basic in Clinical Nutrition“ 3rd edition, Galen (Prague), 2004
Lipid Peroxide Formation: Vitamins (NICU)

**Intralipid 20% ± Vitalipid Infant (A,D₂,K₁,E)**
- Light-protecting tubings; syringe pump
- FOX Assay: tert-butyl hydroperoxide (TBH) as reference

**Graph:** Trend in peroxide formation in a lipid emulsion with (1, a, b, ab) and without fat soluble vitamins (contr.).

The emulsion was pumped through the orange coloured infusion system at different flow and lighting conditions.

Gräflein, Mühlebach, Clinical Nutrition 2004;23:892
Drug Nutrient Interaction
Ciclosporin (Sandimmun®) admixed to i.v. Intralipid®

Fig. 1: Lipase inactivation by CyA, Sandimmun™i.v. or solvent in lipid emulsion. Solvent (CyA-free) is expressed corresponding to the concentration in Sandimmun™i.v.

Clinical Nutrition, 2001;20(S3):27
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# PN Delivery Systems: 3-C Bags

<table>
<thead>
<tr>
<th></th>
<th>Bottles with single components</th>
<th>Bottles with combined components</th>
<th>Two in one Admixtures</th>
<th>All-in-one (3 in 1) admixtures</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Amino acids</strong></td>
<td>![Icon]</td>
<td>![Icon]</td>
<td>![Icon] 2:1</td>
<td>![Icon]</td>
</tr>
<tr>
<td><strong>Glucose</strong></td>
<td>![Icon]</td>
<td>![Icon]</td>
<td>![Icon] 2:1</td>
<td>![Icon]</td>
</tr>
<tr>
<td><strong>Lipid</strong></td>
<td>![Icon]</td>
<td>![Icon]</td>
<td>![Icon] 2:1</td>
<td>![Icon]</td>
</tr>
<tr>
<td><strong>Ready-to-use</strong></td>
<td><strong>(-)</strong></td>
<td><strong>(+)</strong></td>
<td><strong>+</strong></td>
<td><strong>++</strong></td>
</tr>
</tbody>
</table>

Adapted from „Basic in Clinical Nutrition“ 3rd edition, Galen (Prague), 2004
Pharmacist’s Role
Safe Practices

Pharmacist’s Role: PN as Drug Vehicle
# Quality of Hospital PN Use:
## Concordance to local guidelines

92/113 consecutive surgical patients with PN, prospective analysis over 9 months

## Results

<table>
<thead>
<tr>
<th>Category</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of PN [d]</td>
<td>7-78 (min-max) 14 (mean) 12 (median)</td>
</tr>
<tr>
<td>Indication</td>
<td>Guidelines (ASPEN ´93) 77% (71/92) fulfilled</td>
</tr>
<tr>
<td>Chart Review (Check lists)</td>
<td>Requirements Prescriptions Lab tests 50% fulfilled</td>
</tr>
<tr>
<td></td>
<td>Lab tests 64% incomplete</td>
</tr>
<tr>
<td>Complications</td>
<td>Hyperglycaemia 30% (&gt; 10mM)</td>
</tr>
<tr>
<td></td>
<td>Catheter-related 7% (2/3 infections)</td>
</tr>
</tbody>
</table>

Quality Increase of PN Treatment

Nutrition Guidelines
(Nutrition Support Team)

- Standardisation of PN treatments (unified concept)
- Less inappropriate treatments (errors ↓)
- Reduced costs

Adapted from Woolf SH, Arch Intern Med 1992;152:946-52
**PN: Economic Importance in Hospitals**

<table>
<thead>
<tr>
<th>Drug Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basic i.v. Fluids for infusion</td>
</tr>
<tr>
<td><strong>Parenteral Nutrition</strong></td>
</tr>
<tr>
<td>Dalteparin (LMWH, Coagulation disorders)</td>
</tr>
<tr>
<td>Rituximab (MabThera® Antineoplastics)</td>
</tr>
<tr>
<td>Gamma Globulines i.v. (Immunology)</td>
</tr>
<tr>
<td>Iopromid (Ultravist® Constrat media)</td>
</tr>
<tr>
<td>Trastuzumab (Herceptin® Antineoplastics)</td>
</tr>
<tr>
<td>Erythropoetin (Hemodialysis)</td>
</tr>
<tr>
<td>Docetaxel (Antineoplastics)</td>
</tr>
<tr>
<td>Piperacillin + Tacobactam</td>
</tr>
<tr>
<td>Paclitace (Antineoplastics)</td>
</tr>
<tr>
<td>Carboplatin (Antineoplastics)</td>
</tr>
<tr>
<td>Gemcitabin (Antineoplastics)</td>
</tr>
<tr>
<td>Iomeprol (Iomeron® Constrat media)</td>
</tr>
<tr>
<td>Infliximab (Remicade®)</td>
</tr>
<tr>
<td>Cisplatin (Antineoplastics)</td>
</tr>
<tr>
<td>Hemodialysis Concentrates (Hemodialysis)</td>
</tr>
<tr>
<td>Amoxicillin + Clavulansäure (Anti-Infection)</td>
</tr>
</tbody>
</table>

(Pharmacy KSA Acquisition Costs 2004)
Pharmaconutrition
Different Types of Lipid Emulsion

- Soybean / Safflower Oil (Ω-6 : Ω-3 ~ 7 : 1)
  Arachidonic acid ➔ PEG$_{2;4}$ LT$_{2;4}$ (SIRS)

- MCT / LCT (Ω-6 : Ω-3 ~ 7 : 1)
  Structured Lipid Emulsion

- SMOF (Ω-6 : Ω-3 ~ 2.5 : 1)
  Soybean (30%)-MCT (30%)-Olive Oil (25%)-Fish Oil (15%) EPA, DHA

i.v. Drug Errors at Ward Level
Admixing & Administration

Identification (prescription) (3%)

Ready to use (0%)

1-step (0%)

Multi-step (14%)

Identification Patient (0%)

Bolus (73%)

Small volume Infusion (9%)

Large volume Infusion (0%)

Incompatibility reactions

Chemical Incompatibilities

- Oxidation / Reduction
- Hydrolysis
- Polymerisation
- Decarboxylation (CO$_2$ formation)
- Racemate formation
- Complexation