Parenteral Nutrition Preparation

1

Admixture Types

- 2-in-1
  - Dextrose + amino acids + micronutrients
  - Fat emulsion separately infused
- 3-in-1
  - Dextrose + amino acids + micronutrients + fat emulsion
  - Often referred to as TNA (total nutrient admixture)

2

Admixture Types

2-in-1

3-in-1 (TNA)

aspen LEADING THE SCIENCE AND PRACTICE OF CLINICAL NUTRITION
American Society for Parenteral and Enteral Nutrition

3

Advantages of TNAs

Advantages

All components aseptically compounded by the pharmacy
Preparation is more efficient for pharmacy personnel, especially if automated
Less manipulation of the system during administration
Less risk of contamination during administration
Inhibited or slower bacterial growth if contamination does occur compared to separate IVFE
Less nursing time needed for one container per day and no piggyback IVFE to administer
Less supply and equipment expense for only one infusion pump and IV tubing
More convenient storage, fewer supplies, easier administration in home care settings
Dextrose and venous access tolerance may be better in some situations
Possible applications in fluid-restricted patients because IVFE 30% is restricted to use in TNA
May be more cost-effective overall in certain settings
Fat clearance may be better when IVFE is administered over more than 12 hours

[illegible]

aspen LEADING THE SCIENCE AND PRACTICE OF CLINICAL NUTRITION
American Society for Parenteral and Enteral Nutrition

4

Disadvantages of TNAs

Disadvantages

- Larger particle size of admixed IVFE precludes use of 0.22-micron (bacteria-eliminating) filter, and requires larger pore size filter of 1.2 microns
- Admixed IVFE less stable, more prone to separation of lipid components
- Formulations are more sensitive to destabilization with certain electrolyte concentrations
- Formulation more sensitive to destabilization with low concentrations of dextrose and amino acids
- Lower pH amino acid formulations may destabilize the IVFE-portion of admixture
- Formulation may be unstable when the final concentration of IVFE is low
- Difficult to visualize precipitate or particulate material in the opaque admixture
- Certain medications are incompatible with IVFE portion of admixture
- Catheter occlusion more common with daily IVFE
- Less stable over time than dextrose–amino acids PN formulations with separate IVFE

[illegible]

aspen LEADING THE SCIENCE AND PRACTICE OF CLINICAL NUTRITION
American Society for Parenteral and Enteral Nutrition

5

What do we do in the real world?

- Most pediatric hospitals use 2-in-1's
  - May not have enough fat for stable emulsion and more prone to "crack" because of lower pH
  - Increased Calcium-Phosphorus needs so greatly potential for precipitation
  - More likely to have limited access and thus more likely to have incompatibility issues
  - Worried about infection risk
    - Should only hang lipids over 12hrs if drawn up into new container (i.e., syringe) from original containers
- Adult hospitals use both methods depending on hospital standards

aspen LEADING THE SCIENCE AND PRACTICE OF CLINICAL NUTRITION
American Society for Parenteral and Enteral Nutrition

6

Storage/Compounding – General Principles

- Each component of PN prescription should be reviewed to ensure balanced PN formulation is provided
- Each component assessed for dose and potential compatibility problems
- All compounded PN formulations should be visually inspected to ensure no gross contamination or precipitation present
- Should follow manufacturer's compounding sequence to ensure safety of preparation

aspen LEADING THE SCIENCE AND PRACTICE OF CLINICAL NUTRITION
American Society for Parenteral and Enteral Nutrition

7

Storage and Compounding

- Require stringent cleanroom requirements (according to USP <797>)
  - Medium risk

TABLE 15-6 Risk Level Classification and Beyond-Use Dating Guidelines for Compounded Sterile Preparations (CSPs)

Risk Level	Example(s)	Beyond-Use Dating	
		Room (20–25°C)	Refrigeration (2–8°C)
Low	Reconstitution of a single dose vial of lyophilized powder with a sterile diluent for transfer into another container (eg, pediatric parenteral multivitamins)	48 hours	14 days
Medium	Mixing of multiple manufactured additives for transfer into a large-volume parenteral solution (eg, PN formulations)	30 hours	9 days
High	Preparation of nonsterile powder for intravenous infusion (eg, extemporaneously compounded L-glutamine for supplementation in PN formulation)	24 hours	3 days

[illegible]

- Follow manufacturer's instructions

8

Storage and Compounding

- Compounder vs. dual-chamber bags
  - Compounder provides individualized therapy
    - Self
      - Flexibility of timing
      - Increased requirements, cost
    - Outsource
      - Inflexibility of timing
      - Compounding and its requirements are someone else's problems
  - Dual-chamber bags provide convenience

9

Compounder

http://pharmacorner.com/default.asp?action=article&ID=892

10

Dual-chamber = Clinimix

- http://www.clinimix.com/about

http://www.prestoimages.net/store/rd648/648_pd2008418_1.jpg

11

Compounding Order Example

- 1st combine amino acids, dextrose, sterile water for injection
- 2nd add electrolytes
  - 1st electrolyte should be phosphorus salt(s)
  - Last electrolyte should be calcium gluconate
- 3rd add vitamins and trace elements
- Inspect for particulate matter/precipitation
- Last add IVFE (if TNA)

aspen LEADING THE SCIENCE AND PRACTICE OF CLINICAL NUTRITION
American Society for Parenteral and Enteral Nutrition

12

Stability vs. Compatibility

- Stability refers to
  - Degradation of nutritional components that changes its original characteristics
    - Maillard reaction → occurs between IV dextrose and such amino acids as lysine, resulting in brownish discoloration of the final formulation
  - Ability of PN additives, including medications, to maintain their chemical integrity and pharmacological activity
    - Photodegradation caused by light exposure, particularly fluorescent light, results in loss of some vitamins, including cyanocobalamin, folic acid, phylloquinone, pyridoxine, riboflavin, thiamin, and retinol

13

Stability vs. Compatibility

- Compatibility involves formation of precipitates
  - Can be solid, such as crystalline matter, or liquid, such as phase separation of oil and water in a TNA
  - Majority of studies evaluating additive and Y-site compatibility with PN formulations evaluate only physical compatibility; few include stability
  - Can be different between a 2-in-1 and 3-in-1 due to presence of fat emulsion

14

Stability and Compatibility Issues

- Fat emulsion in TNA (3-in-1)
- Calcium-phosphorus
- Medications

15

Fat Emulsion in TNA

- IVFE consists of interior oil phase dispersed in external water phase
- Polar and nonpolar regions on same fat droplet are responsible for maintaining stability
- Polar regions create negative charge, or zeta potential, on the surface of the fat droplet that promotes repulsion between neighboring lipid particles of the same charge
- When surface charge becomes less negative, fat droplets begin to aggregate into larger fat globules (greater than 1 micron in diameter), and emulsion becomes unstable
- Clinically, IVFE becomes unsafe for administration at this point, and fat globules may lodge in pulmonary vasculature, compromising respiratory function
- Factors that may alter electrical charge on fat droplet surface include reductions in pH and addition of electrolyte salts
- Preferred pH range of 6 to 9
    - Outside of range may irreversibly destabilize or “crack” emulsion

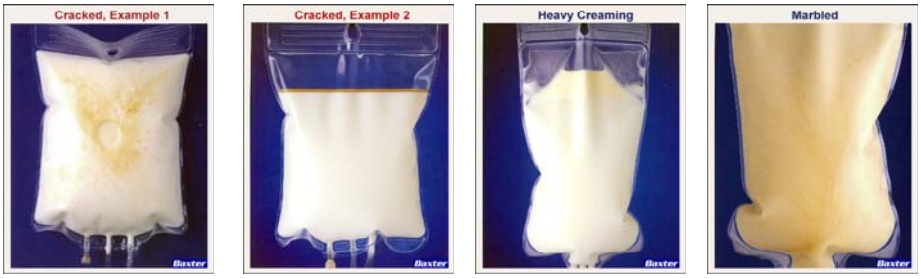
16

"Cracked" TNA???

- Oil phase separates from water phase and first appears as subtle changes in uniformly white appearance of the emulsion which may progress to yellow oil streaks throughout the bag or development of amber oil layer at top of admixture bag

17

aspen LEADING THE SCIENCE AND PRACTICE OF CLINICAL NUTRITION
American Society for Parenteral and Enteral Nutrition



18

aspen LEADING THE SCIENCE AND PRACTICE OF CLINICAL NUTRITION
American Society for Parenteral and Enteral Nutrition

Calcium-Phosphorus

- In 1994, FDA released safety alert in response to reports of two deaths and at least two cases of respiratory distress associated with administration of PN formulations thought to contain insoluble or unstable intermediate (i.e., calcium phosphate crystals)
- Diffuse microvascular pulmonary emboli containing calcium phosphate were confirmed upon patient autopsies
- Calcium-phosphate solubility is major compatibility concern with PN formulations
- Prescribers must be familiar with limitations for addition of calcium and phosphate
- Compounding pharmacist is then a secondary check for calcium- phosphate solubility

aspen LEADING THE SCIENCE AND PRACTICE OF CLINICAL NUTRITION
American Society for Parenteral and Enteral Nutrition

19

Calcium-Phosphorus

TABLE 15-8 Factors That Influence Calcium and Phosphorus Compatability in PN Formulations

Amino acids concentration
Amino acids product composition (ie, pH or phosphorus content)
Calcium and phosphate concentrations
Calcium salt form
Dextrose concentration
pH of formulation
Temperature of formulation
Order of mixing additives

Adapted with permission from Trissel LA. *Trissel's Calcium and Phosphate Compatibility in Parenteral Nutrition.* Houston, TX: TriPharma Communications; 2001, © Lawrence Trissel.

aspen LEADING THE SCIENCE AND PRACTICE OF CLINICAL NUTRITION
American Society for Parenteral and Enteral Nutrition

20

Medications

- Precipitates from medication incompatibilities or emulsion disruption from medication additives
- Studies of medications with 2-in-1 and TNA PN formulations during simulated Y-site administration have been performed
  - Incompatibilities ranged from formation of precipitates, to haziness, discoloration, and emulsion disruption with frank separation of oil and water phases
- Compatibility by Y-site infusion (co-infusion) is not synonymous with admixture into PN formulation because time of exposure between medication and PN components is greatly increased with admixture
- Additionally, pharmacokinetic variables must be considered with admixture of medication into PN because medication must be safe and effective when administered as continuous infusion or over cycle time of PN formulation

21

aspen LEADING THE SCIENCE AND PRACTICE OF CLINICAL NUTRITION
American Society for Parenteral and Enteral Nutrition