I/V admixtures

Dr. Abdalkareem Maghmomeh
Faculty of Pharmacy- Hama University

Lecture 10

I/V admixtures

- **An IV admixture** is the preparation of a pharmaceutical mixture of two or more drugs into a large bag or bottle of IV fluid.
- This is always done under the direction of a doctor, controlled/performed by a trained pharmacists.
- This is to be sure that no one is accidentally overdosed, or given the wrong medications.

IV route

In iv admixtures or in the form of iv infusions it is a suitable method to **administer large volume** of infusion, total parenteral nutrition, of drug in the form of iv admixtures.

Intravenous Preparations

- The IV route of administration is used
  1. to reach appropriate drug **serum** levels
  2. for drugs with **unreliable gastrointestinal** (GI) absorption
  3. for the patient who can have **nothing by mouth**
  4. for the patient who is **unconscious or uncooperative**, and for rapid correction of fluid or electrolytes
- Most parenterals are introduced directly into the bloodstream

  must be free of **air bubbles** or particulate matter

  have many characteristics including solubility, osmolality, and pH

Characteristics of IV Preparations

- Intravenous (IV) preparations are either:
  - solutions (in which ingredients are dissolved)
  - suspensions (in which ingredients are suspended)
- Most parenteral preparations are made of ingredients in a sterile water medium
- Some parenteral preparations may be oleaginous (oily)

Characteristics of IV Preparations

- Parenteral IV preparations must have chemical properties that will not
  - damage vessels or blood cells
  - alter the chemical properties of the blood serum

- With blood, IVs must be
  - iso-osmotic (having the same number of particles in solution per unit volume)
  - isotonic (have the same ***osmotic pressure***, meaning the pressure produced by or associated with osmosis)

Characteristics of IV Preparations

- The *osmolality* is the amount of particulate per unit volume of a liquid preparation
  - measured in milliosmoles (mOsm)
  - osmolality of blood serum = 285 mOsm/L
- An *isotonic solution* is a solution in which body cells can be bathed without a net flow of water across a semipermeable membrane
  - 0.9% normal saline (NS)

Characteristics of IV Preparations

- The ***pH value*** is the degree of acidity or alkalinity of a solution
  - acidic solution: pH of less than 7
  - alkaline solution: pH value more than 7

- Human blood plasma has a pH of 7.4
  - slightly alkaline
  - parenteral IV solutions should have a pH that is neutral (near 7)

Characteristics of parenteral preparations that are important to adjust:

- Osmolality
- pH are characteristics of parenteral preparations.

- It is important that they be adjusted to be as close as possible to the values for human blood, to prevent damage to blood cells and organs.

IV infusion is used to deliver

– blood
– water
– other fluids
– electrolytes
– drugs
– nutrients

PARENTERAL NUTRIENT

- Parenteral nutrient formulations are very complex mixtures containing:
  - carbohydrate, protein, lipid (are available from various manufacturers.)
  - water, electrolytes, vitamins, and trace minerals.

Water

- sterile water for injection
- dilute the macronutrients to achieve the prescribed final concentrations of dextrose, amino acids, and lipids, as well as the final volume of the parenteral nutrient formulation.

Carbohydrate

- Dextrose in water is the most common carbohydrate for IV use.
- available in concentrations ranging from 2.5% to 70%.
- These dextrose solutions:
  - mixed with other components of the parenteral nutrient formulation
  - diluted to various final concentrations.
  - From these concentrations of dextrose, all parenteral nutrient formulations can be compounded.
- IV dextrose is monohydrated and provides 3.4 kcal/g, in comparison with dietary carbohydrate, which has a caloric density of 4 kcal/g

Lipid

- Lipid for IV use is supplied as :
  - emulsions of either soybean oil (10%, 20%, and 30%.)
  - or a 50:50 physical mixture of soybean and safflower oils that provide long-chain fatty acids (>16 carbon length). as 10% and 20%.
- The 10% and 20% IV lipid emulsions may be:
  - administered concurrently (IV piggyback) with dextrose/amino acid solutions
  - or admixed with dextrose and amino acids.

Lipid

  - has a caloric density of 9 kcal/g
  - But the caloric density increased to 10 kcal/g by the addition of glycerol, which is added to adjust the osmolarity.
- Egg phospholipids:
  - added as emulsifiers.
  - contraindicated in patients with **severe egg allergies**, especially egg yolk allergies (derived from egg yolks).
  - contribute to 15 mmol/L of phosphorus.
- Medium-chain triglycerides (MCTs):
  - provide 8.3 kcal/g.

Protein

- available as synthetic amino acids
- serves as the source of nitrogen.
  - Nitrogen is the building block of cell structure
  - used to produce enzymes, peptide hormones, and serum proteins.
- Amino acid concentrations
  - 3.5% to 20%
  - vary slightly from one product to another in the specific amounts of each amino acid, electrolyte content, and pH

Protein

- Generally, amino acid products are characterized as:
  - “standard” mixtures, which provide a balanced mix of essential, nonessential, and semiessential amino acids
  - or “specialty” mixtures, which are modified for specific disease states.
  - For example, the specialty amino acid mixture for use in patients with hepatic failure contains increased amounts of the **branched-chain amino acids** and decreased amounts of the aromatic amino acids.

- for critically ill patients
  - Protein formulations supplemented with **branched-chain amino acids** with normal amounts of the other amino acids.
- for renal failure:
  - Amino acid products have **increased amounts of the essential amino acids**
  - or provide only essential amino acids
- for neonates
  - Amino acid products designed **to meet their special needs**
- Protein or amino acids have a caloric density of 4 kcal/g.
  - Protein calories have not always been included in the calculation of energy needs for patients receiving parenteral nutrient formulations.
  - Ideally, protein is used to:
    - stimulate protein synthesis and tissue repair
    - not oxidized for energy.

Micronutrients

- Micronutrients are the electrolytes, vitamins, and trace minerals needed for metabolism.
- These nutrients:
  - available from various manufacturers as either single entities or in combinations.
  - E.g. zinc is available commercially as a single trace element product or as a combination product with the other trace elements: copper, chromium, manganese, and selenium.
- Be careful to available specific products to avoid providing inadequate or excessive amounts

FORMULATION DESIGN

Macronutrients and Micronutrient

- Caloric goal was 1,300 kcal/day and 60 g protein/day.
  - Giving 60 g of protein per day would provide 240 kcal/day (1 g protein = 4 kcal).
  - total desired calories - protein calories = nonprotein calories (to be provided by carbohydrates and fat) needed.
  - this would be 1,300 total calories – 240 protein calories = 1,060 nonprotein calories needed.
- Typically:
  - Dextrose: 60% to 70% of nonprotein calories
  - Lipids: remaining 30% to 40% of nonprotein calories.
- Providing her with 742 kcal of dextrose (218 g of dextrose; 1 g dextrose = 3.4 kcal) would supply 70% of nonprotein calories as dextrose.
- The remaining 30% of nonprotein calories would be provided by lipids at 318 kcal (31.8 g of lipids; 1 g of IV lipids= 10 kcal).

The formula adjusted based on patient response and tolerance.

- If she had complications of hyperglycemia, the dextrose component could be reduced with a subsequent increase in the lipid proportion of nonprotein calories.
- If hypertriglyceridemia resulted, the lipid component may be reduced with a subsequent increase in dextrose.

- Her nutrient formulation should contain standard amounts of electrolytes, and daily dose of IV multivitamins and trace elements

- **Additional fluid must be provided** for increased losses such as vomiting, diarrhea, or large open wounds.
- The extra fluid intake may put patients at risk for becoming fluid overloaded, manifesting as hypervolemic, hypotonic hyponatremia.
- Therefore, she should be monitored for signs of fluid overload:
  - peripheral edema
  - shortness of breath
  - daily intake exceeding daily output
  - hyponatremia
  - rapidly increasing weight

Essential fatty acid deficiency

- A small amount of lipid is necessary **to prevent** essential fatty acid deficiency (EFAD).
- The essential fatty acids:

  linoleic and alpha-linolenic, are those that cannot be synthesized by humans.
- This occur because
  - hypertonic dextrose associated with high circulating concentrations of insulin.
  - insulin promotes lipogenesis rather than lipolysis, linoleic acid cannot be released from adipose tissue.

- **Clinical symptoms of EFAD:**
  - dry, thickened, scaly skin
  - hair loss
  - poor wound healing
  - Thrombocytopenia (after a few weeks to months of lipid-free parenteral feedings).
- **The requirement** is 1% to 4% of total caloric intake
  - So give 500 mL of a 10% lipid emulsion twice weekly .
  - infused at a rate of <0.1 g/kg/hour to prevent :
    - Impairment in hepatic, pulmonary, immune, and platelet functions

Stability

- IV lipid emulsions alone gradually break down over time because of increased formation of free fatty acids and a resultant decrease in pH.
- When lipids are mixed with dextrose and amino acids, this process is **enhanced**.
- IV lipid products available as an **anionic egg yolk phosphatide emulsifier**, which stabilizes the lipid droplets of the dispersed phase with the aqueous external phase and maintains the integrity of the dispersion.

- The addition of any substance with **cationic properties** (divalent cations (Mg^{2+}, Ca^{2+}):
  - neutralize the negative charge of the emulsifier
  - alter the emulsion's stability
  - increase fat particle size
- When the emulsion becomes unstable, the fat particles begin to aggregate and the particle size increases:
  - begin with creaming
  - end with the coalescence of the lipid particles, or "cracking" of the emulsion.

- After preparation, it should be refrigerated (4◦C) to preserve stability.
- Once it is taken from the refrigerator, it may be warmed to room temperature and the contents mixed well before administration.
  - gently invert the container up and down to ensure top to-bottom transfer of the fluid.
  - Strong shaking should be avoided because it introduces air, which can destabilize the emulsion.

Microbial growth

- Dextrose/amino acid formulations are not conducive to growth of most organisms because of their high osmolarity (>2,000 mOsm/L) and acidic pH.

- Lipid emulsions alone are isotonic and have a physiologic pH, providing an optimal growth medium.

Guidelines for Daily Electrolyte Requirements

- Electrolyte Amount
  - Sodium 80–100 mEq
  - Potassium 60–80 mEq
  - Chloride 50–100 mEq
  - Acetate 50–100 mEq
  - Magnesium 8–20 mEq
  - Calcium 10–15 mEq
  - Phosphorus (phosphate) 20–40 mmol

Recommended Adult Daily Doses of Parenteral

- Fat-Soluble Vitamins

A	3,300 IU
D	200 IU
E	10 IU
K	150 mcg

- Water-Soluble Vitamins

Thiamine (B1)	6 mg
Riboflavin (B2)	3.6 mg
Niacin (B3)	40 mg
Pyridoxine (B6)	6 mg
Cyanocobalamin (B12)	5 mcg
Folic acid	600 mg
Pantothenic acid	15 mg
Biotin	60 mcg
Ascorbic acid (C)	200 mg

Complications of parenteral nutrition

Re-feeding syndrome

- severe hypophosphatemia with other metabolic complications:
    - Hypokalemia
    - Hypomagnesemia
    - vitamin deficiencies
    - fluid intolerance
    - glucose alterations
- Complications coinciding with refeeding:
    - hypertension, cardiac insufficiency, seizures, coma, and death.

PATHOGENESIS OF REFEEDING SYNDROME

In the starved, there is a loss of lean body mass, water, and minerals.

- Individuals may preserve some intracellular electrolytes, including phosphorus.
- When these individuals are given a concentrated source of calories, the carbohydrates are converted to glucose.
- Glucose, in turn, results in the secretion of insulin.
- The release **of insulin enhances the uptake** of glucose, water, phosphorus, and other intracellular electrolytes.
- The combination of phosphorus depletion and intracellular uptake causes severe hypophosphatemia.

- **Clinical signs of hypophosphatemia**:
  - occur when serum concentrations fall below 1.0 mg/dL
  - lethargy, muscle weakness
  - impaired WBC function
  - glucose intolerance
  - seizures
  - hemolytic anemia
  - death
- Moderate to severe, complicated hypophosphatemia can be managed by administering up to 0.625 mmol/kg of phosphate IV.

To minimize the risk of re-feeding syndrome

- all electrolyte abnormalities must be corrected before any nutrition is initiated.

- Nutrition used slowly and vitamins administered routinely.

- Electrolytes, including phosphorus, potassium, magnesium, and glucose, should be monitored at least daily over the first week.

What potential complications could result from overfeeding

- Overfeeding should be avoided in all patients, especially those with respiratory concerns (i.e., mechanically ventilated, chronic obstructive airway disease).
- Overfeeding with carbohydrates is particularly detrimental because of the amount of CO_2 produced relative to the amount of O_2 consumed.
- This results in CO_2 retention that may **lead to acid–base disturbances.**
- Complete oxidation of carbohydrate is demonstrated at dextrose infusions **of 4 to 5 mg/kg/minute.**
- Infusions exceeding this rate increase CO_2 production and may cause respiratory distress.

Hypokalemia

- a common metabolic abnormality occurs within 24 to 48 hours.
- Causes
  - Potassium moves, along with dextrose, from the extracellular to the intracellular space.
  - building lean body mass (i.e., anabolism) requires 3 mEq of potassium / gram of nitrogen .
  - Administering dextrose promotes repletion of glycogen stores, which also requires potassium.

Hypomagnesemia

- Magnesium is **primarily an intracellular cation** and is considered an **anabolic electrolyte**.
- Synthesis of lean tissue requires 0.5 mEq magnesium per gram of nitrogen.

Hyperglycemia

- common metabolic complication, especially in stressed patients.
- The maximum rate of dextrose metabolism is 4-7 g/kg/day.
- In doses of >7 g/kg/day, dextrose is used inefficiently and is converted to fat that lead to:
  - respiratory compromise and hepatic dysfunction
  - Hyperglycemia is associated with:
    - electrolyte and acid–base disturbances
    - osmotic diuresis
    - increased risk of infections (especially *Candida albicans*)
    - altered phagocyte and complement function.
    - In extreme cases, progresses to hyperosmolar, nonketotic acidosis and coma (40% mortality).

- frequently monitoring blood glucose concentrations
- advancing therapy only when:
  - the serum glucose is <150 mg/dL for stable patients
  - <120 mg/dL for critically ill patients.

- Insulin therapy should be given if serum glucose concentrations exceed these parameters

calcium and phosphate incompatibilities

- a “corrected” calcium formulation may be used.

- Administering a formulation containing calcium phosphate crystals may block blood flow, especially in the lungs, and associated with respiratory distress and death.

- Using calcium gluconate can enhance calcium phosphate solubility.

- The in vitro precipitation of calcium phosphate depends on:
  - calcium salt
  - concentrations of calcium and phosphate
  - amino acid concentration
  - Temperature
  - pH of the formulation
  - infusion time.

- calcium and phosphate should not be added to formulation in close sequence.
  - add phosphate first and then calcium
- Other guidelines for improving the solubility of calcium are a final amino acid concentration of >2.5% and a pH <6.

- increase in the temperature can enhance precipitation of calcium phosphate.

- Formulations should be infused :
  - within 24 hours after preparation if stored at room temperature
  - if refrigerated, they should be infused within 24 hours after rewarming.

- slow infusions may decrease solubility.

Medication Additives

- The stability of medications when mixed with formulations is a complex issue.

- Some medications may be added directly to the parenteral nutrient formulation, whereas others should be administered via a secondary infusion set

- This area of knowledge is growing rapidly, and current information regarding compatibility and stability is available in standard references such as Trissel's Handbook of Injectable Drugs.

- Although insulin, antibiotics, chemotherapeutic agents, H2-receptor antagonists, and heparin have been added to formulations in some specific conditions, the routine addition of medications to parenteral nutrient formulations is discouraged(غير مستحبة).

MONITORING PARAMETERS

- Daily monitoring parameters:
  - vital signs
  - body weight
  - serum chemistries
  - hematologic indices
  - nutrition intake
  - fluid intake and output.
- The adequacy of nutrition therapy should be assessed weekly.
- measuring serum concentrations of visceral proteins

Routine Monitoring Parameters for Parenteral Nutrition

- Before Initiating Therapy
  - Body weight
  - Serum electrolytes (Na, K, Cl, HCO_3^-, BUN, creatinine)
  - Glucose
  - Ca, Mg, P
  - Albumin
  - Triglycerides
  - Complete blood count
  - Liver-associated tests (AST, ALT, alkaline phosphatase, bilirubin)
  - Prothrombin time

- **Daily**
  - Body weight
  - Vital signs (pulse, respirations, temperature)
  - Fluid intake
  - Nutritional intake
  - Output (urine, other losses)
  - Serum electrolytes (Na, K, Cl, HCO_3^-, BUN, creatinine)
  - Glucose

- **Two or Three Times a Week**
  - CBC
  - Ca, Mg, P
- **Weekly**
  - Albumin
  - Liver-associated tests (AST, ALT, alkaline phosphatase, bilirubin)
  - prothrombin time
  - Nitrogen balance

ELEVATED LIVER-ASSOCIATED ENZYMES

ELEVATED LIVER-ASSOCIATED ENZYMES

- common in adults
- 2 to 3 weeks after beginning therapy.
- usually mild and temporary
- do not progress to significant liver dysfunction
- rarely proceed to hepatic failure.
- Liver-associated enzyme elevations usually resolve when parenteral nutrition therapy is discontinued.

- **Other contributing factors to liver dysfunction:**
  - overfeeding with high amounts of carbohydrate
  - amino acid deficiencies
  - excess fat, EFAD
  - toxic effects of the amino acid degradation products
  - bacterial overgrowth in the small intestine, and lack of stimulation of the GI tract.
- **Potential treatments include**
  - metronidazole
  - ursodeoxycholic acid
  - Choline
  - carnitine.

USE OF PARENTERAL NUTRITION IN SPECIAL DISEASE STATES

Hepatic Failure

- Patients with chronic hepatic failure (esp.alcohol-induced disease) are malnourished and prone to complications such as GI bleeding and infection.
- The metabolism of glucose, fat, and protein is altered in liver disease.
- Amino acid metabolism is particularly affected because blood is shunted around the liver.
- adequate protein:
  - must be provided to support regeneration of the liver and other vital functions such as the immune system.

Renal Failure

- The protein dose in acute renal failure should be reduced to 0.6 to 1 g/kg/day:
  - the kidneys have a limited ability to excrete nitrogenous byproducts of protein metabolism

- The use of essential amino acids (EAAs) orally improve uremic symptoms

- the loss of amino acids across the dialysis filter, which can range from 20 to 28 g of nitrogen per day.
  - Sufficient amino acids should be provided to reward for this daily loss
  - Protein requirements for patients on dialysis may be as high as **2.5 g/kg/day**.
- the rapid loss of electrolytes must be considered.
  - Patients may decreases in potassium, magnesium, and phosphorus
  - This requires frequent monitoring and replacement of these electrolytes, usually as IV supplements

Short Bowel Syndrome

- characterized by maldigestion, malabsorption, dehydration, and both macronutrient and micronutrient abnormalities.
- adaptive period:
  - may take several weeks to months to years.
  - enhanced by stimulation of the enterocytes with nutrients, which is best provided by small, frequent oral meals or tube feeding.
- After extensive small bowel resection, patient may experience severe diarrhea that lead to:
  - dehydration and electrolyte abnormalities, including hyponatremia, hypokalemia, hypomagnesemia, hypocalcemia, and metabolic acidosis.

- managing fluid and electrolyte imbalances
- H2-receptor antagonists (decreasing gastric secretion)
- For diarrhea
  - Antimotility agents
- Vitamin supplementation
- trace minerals (particularly zinc and selenium)

pancreatitis

- IV lipid emulsions are a safe and efficacious form of calories for patients with pancreatitis because.
  - oral fats ingestion may stimulate pancreatic exocrine function
  - Although hyperlipidemia seen with alcohol-induced pancreatitis.
  - Hypertriglyceridemia associated with acute pancreatitis is most seen in hereditary or acquired defects in lipid metabolism.
  - pancreatitis alone may be associated with hypertriglyceridemia

- Monitoring serum triglyceride should be part of routine management for patients with pancreatitis and those receiving parenteral nutrient formulations containing lipids.
- Serum triglyceride concentrations should be maintained at <400 mg/dL with a continuous infusion of lipids and <250 mg/dL when checked 4 hours after the infusion for patients receiving intermittent lipid infusions.
- If serum concentrations exceed these parameters, consideration must be given to decreasing or eliminating the IV lipid from the parenteral nutrient regimen