به نام خدا

فارماکوویژیللانس و عوارض ناخواسته داروها

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Volume disorders

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FLUID CONTENT OF THE BODY

- Varies with age, sex, adipose tissue
- Females 45-50% TBW
- Males 50-60% TBW
- Infants 77% TBW
RULE OF THIRDS

1. Intracellular: 2/3 (40% TBW)
2. Extracellular: 1/3 (20% TBW)
   a. Interstitial + Lymph: 2/3 (15% TBW)
   b. Intravascular: 1/3 (5% TBW)
Hypervolemia
1- What is hypervolemia?

- Hypervolemia results from a state of *positive balance of sodium and water* that produces expansion of the ECF.
- Most often, hypervolemia is caused by renal retention of sodium (Na) and water.
- This retention can be primary or secondary
1- What is hypervolemia?

- *Primary renal sodium retention* is caused by renal diseases and conditions characterized by primary excess mineralocorticoid activity.
1- What is hypervolemia?

- *Secondary hypervolemia* is associated with a 
  reduction in the effective arterial volume (EAV)

- Three most common conditions are:
  - CHF
  - Nephrotic syndrome
  - Cirrhosis

- In each of these disorders the body perceives the reduced EAV and the homeostatic mechanisms respond as if there is hypovolemia, causing the kidney to retain Na and water thereby producing ECF volume expansion.
2- What are the manifestations of hypervolemia?

- **Edema** is the most common clinical manifestation of hypervolemia; in fact, the terms are generally synonymous.
2- What are the manifestations of hypervolemia?

- Specific causes can also produce other manifestations:
  - heart failure produces jugular venous distension (normal JVP 6 to 8 cm H₂O) and pulmonary crackles
  - cirrhosis produces ascites
  - nephrotic syndrome produces widespread edema.
3- How is hypervolemia treated?

- There is one key strategy to treat hypervolemia: *inducing a negative sodium (and water) balance*.
- The three methods to accomplish this goal are:
  - dietary sodium restriction
  - Diuretics
  - ECF removal by ultrafiltration
- One can also remove fluid from the abdominal or thoracic space directly (paracentesis or thoracentesis).
4- How do diuretics work?

- Diuretics are classified based on mechanism and site of action

- Five main classes of diuretics:
  1. osmotic diuretics
  2. thiazides (hydrochlorothiazide, chlorthalidone, and metolazone)
  3. loop diuretics (furosemide, bumetanide, torsemide, and ethacrynic acid)
  4. potassium-sparing diuretics (amiloride, triamterene, spironolactone, and eplerenone)
  5. carbonic anhydrase inhibitors
1. Osmotic diuretics
2. Carbonic anhydrase inhibitors
3. Loop diuretics
4. Thiazides
5. Potassium sparing
Key Points

1. The treatment goal for hypervolemia is to induce a negative sodium (and water) balance.
2. The purpose of using diuretics to treat edema is to reduce extracellular fluid volume and maintain it at a clinically acceptable level.
3. A high salt intake can negate the beneficial effects of diuretics.
Hypovolemic
1- What are the extrarenal causes of hypovolemia?

- **Absolute**
  - Bleeding
  - Gastrointestinal fluid loss (diarrhea, vomiting, ileostomy or colostomy secretions)
  - Fluid loss from skin (burns, sweat)
  - Respiratory fluid loss

- **Relative**
  - Third space loss
  - Sepsis
  - Edema states (heart failure, cirrhosis)
2- What are the renal causes of hypovolemia?

- Diuretics
- Partial obstruction or postobstruction etiology
- Endocrine disorders (e.g., hypoaldosteronism, adrenal insufficiencies)
3- Signs and Symptoms

- Change in activities of daily living (ADLs)
- Change in mental status
- Constipation
- Decreased urine output
- Dizziness/faintness
- Postural hypotension
- Tachycardia
- Weakness
- Weight loss (3–5 lb in short time)
4- How does one assess a patient’s volume status?

- Extravascular volume deficits do not become clinically apparent until they exceed **5% of body weight**.
- The symptoms of mild to moderate volume contraction are nonspecific. **Fatigue and lethargy** are the most common.
- More severe volume contraction can produce a **low urine output, postural dizziness, excessive thirst, and cramps**.
- Signs of volume contraction include **tachycardia, dry axillae, orthostatic hypotension** (systolic blood pressure decrease of at least 20 mm Hg or a diastolic blood pressure decrease of at least 10 mm Hg within 3 minutes of standing), and ultimately overt hypotension.
4- How does one assess a patient’s volume status?

- If the volume contraction is prolonged and severe, the GFR can fall with a concomitant *rise in serum creatinine*.

- In such cases the *blood urea nitrogen can be >20 times the creatinine value*, but such a situation may not be present if the person has not been eating.
5- Give some guidelines for volume replacement therapy in hypovolemia

- The *blood pressure and pulse* are the most important parameters to guide the magnitude of fluid replacement
6- Are colloids better than crystalloids for volume replacement?

- For most hypovolemic states, albumin infusion has not been clearly shown to be superior to crystalloids.

- An exception to this general rule is in patients with cirrhosis and tense ascites undergoing large-volume paracentesis; colloids (dextran 70 or albumin) were found to protect against acute kidney injury.

- In patients with severe hemorrhage, administration of packed red blood cells improves tissue perfusion and oxygen carrying capacity.
KEY POINTS: HYPOVOLEMIA

1. Intravascular volume contraction of less than 5% is usually not symptomatic or detectable.

2. The body weight that was lost offers the best estimate of volume losses.

3. There is no proven benefit of usage of colloids over crystalloids for correction of hypovolemia.
Case

- 24 YO M comes to see you complaining that after 2 days of vomiting and diarrhea without fever or abdominal pain or hematochezia that he becomes light headed when standing and thought at one point he was going to pass out.
Case

- What should you document/check?
- How should you treat?
Answers

- What should you document?
  - Orthostatic BP/HR- (pt still hypovolemic?)

- Which type of fluid should you use?
  - Because water and sodium are inherently linked, the assessment of volume status and selection of replacement fluid require examination of sodium concentration.
  - Normal Saline (isotonic) usually is the best
Hypernatremia

- Much less common
  - in hospitalized patients ranges from 0.63% to 2.23%, with the elderly being more susceptible
- Generally means lack of access to water
- Always hyperosmolar
Hypernatremia results in significant morbidity and mortality, *ranging from 42% to 70% in adult patients*.

- Acute elevations of serum sodium above 160 mEq/L are associated with a mortality rate of 75%, whereas mortality in chronic hypernatremia is 10%.
Hypernatremia develops whenever

- Fluid intake is less than the sum of extrarenal and renal water losses or,
- less commonly, when too much salt is introduced without adequate water intake
Hypernatremia

- Defense mechanisms:
  - Kidney
  - Thirst
- Most hypernatremic patients therefore have either an inability to obtain free water or an impaired thirst sensation
Both hypernatremia and hyponatremia can be assessed by the extracellular volume state:

- hypovolemic,
- isovolemic,
- hypervolemic
Hypernatremia always represents a hyperosmolar state, and as such, most of the signs and symptoms are reflections of CNS disturbances.

These include altered mental status, lethargy, seizures, irritability, hyperreflexia, and spasticity.

Patients can also exhibit nausea, vomiting, fever, respiratory distress, and intense thirst.
If symptoms are present and the hypernatremia is thought to be acute in onset, rapid correction over the first several hours is appropriate, with the maximum correction rate not exceeding 2 mEq/L/h.

An accepted goal is to correct half the water deficit over the first 24 hours, with the remaining deficit being corrected over the next 48 hours.
In the setting of hypovolemic hypernatremia, initial management is fluid resuscitation using isotonic saline solutions or other plasma expanders.

Once the intravascular volume has been restored, administration of hypotonic solutions can further restore normal serum tonicity.
For patients with isovolemic hypernatremia, the primary therapy is a hypotonic solution.

- It is important to replace not only the water deficit but also any ongoing fluid losses.

- Water deficit =
  \[0.5-0.6 \times TBW(kg) \times \left[\frac{PNa}{140} - 1\right]\]
The goal of hypervolemic hypernatremia therapy is to promote natriuresis with loop diuretics, along with the administration of 5% dextrose.

If there is significant renal dysfunction, the volume overload and hypertonicity may require dialysis.
**Hypovolemic hypernatremia**

- Correction of volume deficit
  - Administer isotonic saline until improvement of orthostasis, tachycardia, neck veins
  - Treatment for etiology of losses (e.g., insulin, relief of obstruction, removal of osmotic diuretics)

**Euvolemic hypernatremia**

- Correction of water deficit
  - Calculate water deficit (see text)
  - Administer 0.45% saline, 5% dextrose, or oral water, replacing deficit and ongoing losses
  - Follow serum [Na] carefully to avoid water intoxication

**Hyponatremic hypernatremia**

- Removal of sodium
  - D/C offending agents
  - Furosemide
  - Hemodialysis as required for renal insufficiency

**Long-term therapy**

- Central DI
  - See Table 110-2 for pharmacologic therapy
- Nephrogenic DI
  - Correction of [K] and [Ca]
  - Removal of offending drugs
  - Low-sodium diet
  - See Table 110-2 for pharmacologic therapy
A 70 year-old woman who weighs 60 kg is brought to the emergency department from a long-term care facility with a three to four day history of diarrhea. She has had worsening mental status, and her oral intake has diminished. The evaluation in the emergency department reveals a blood pressure of 120/50 mmHg, dry mucous membranes, and a jugular venous pressure below 6 cm H2O. Her serum sodium is 158 meq/L and the serum potassium is normal.
Case

- Increase CVP to 8-12
- The total body water is approximately 40 percent of the lean body weight (it is 50 percent in a hypernatremic man). Thus, the estimated water deficit is $24 \times \left( \frac{158}{140} - 1 \right)$ or 3.1 L.
Hyponatremia
among the most common electrolyte disorders encountered in clinical practice

It is generally associated with hypo-osmolality.

There are, however, clinical settings in which plasma osmolality is normal or even high
Determination of Na Deficit

- Na Deficit = 0.5*W*(N_{\text{desired}}-\text{Na})
- Approximately \textit{one-third} of the deficit can be replaced over the \textit{first 12} hours at a rate of <0.5 mEq/L/hour. The remaining amounts can be administered over the next several days.
Case

- A nonedematous, mildly symptomatic woman who weighs 60 kg (approximately 50 percent of which is water) has a serum sodium concentration of 116 meq/L

- Na deficit?
Case

Sodium deficit = TBW \times 0.5 \times 60 \text{ L} \times \text{desired change in serum sodium}
ELECTROLYTE DISORDERS: POTASSIUM
Primary intracellular cation
98% of total body K reside in the intracellular compartment
Daily intake: 50-100mEq
Elimination: 90% kidney, 10% GI
Different hormonal factors regulate the activity of the Na/K ATPase pump namely Insulin, catecholamines and aldosterone
Normal: 3.5-5 mEq/L
POTASSIUM (K+)

**MOVEMENT INFLUENCED BY:**
- Changes in pH
- Insulin
- Adrenal hormones

**IMPORTANT IN:**
- Neuromuscular irritability
- Intracellular
- Osmotic activity
- Acid-base balance
### Hypokalemia

#### Table 3.4. CAUSES OF HYPOKALEMIA IN THE ELDERLY

<table>
<thead>
<tr>
<th>Inadequate dietary potassium intake</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased gastrointestinal loss</td>
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<tr>
<td>Vernitsing</td>
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<tr>
<td>Diarrhea</td>
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<tr>
<td>Laxative use</td>
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<td>Fistulas</td>
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<tr>
<td>Tube drainage</td>
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<tr>
<td>Increased renal loss</td>
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<tr>
<td>Renal tubular acidosis (proximal and distal)</td>
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<tr>
<td>Thiazide diuretic use</td>
</tr>
<tr>
<td>Loop diuretic use (furosemide, bumetanide, ethacrynic acid)</td>
</tr>
<tr>
<td>Antibiotic use (gentamicin, penicillin, amphotericin B)</td>
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<tr>
<td>Primary hyperaldosteronism</td>
</tr>
<tr>
<td>Secondary hyperaldosteronism (heart failure, cirrhosis)</td>
</tr>
</tbody>
</table>

- Cushing's syndrome
- Exogenous glucocorticoids
- Exogenous mineralocorticoids
- Hyperreninemic renovascular hypertension
- Postobstructive diuresis

#### Transcellular shift

- Alkalosis
- Insulin administration
- Beta-adrenergic agonists

#### Hematologic disorders

- Vitamin B12 treatment of megaloblastic anemia
- Acute myeloid leukemia
Catecholamines

- Beta2 activate Na/K ATPase and cause hypokalemia
Hypokalemia: Causes

- Drugs which may cause hypokalemia
  - Urinary wasting: aminoglycosides, amphotericin B, corticosteroids, diuretics
  - Gastrointestinal losses: laxatives
  - Redistribution: Beta-2 agonists, Insulin
Hypokalemia: Estimation of Deficit

If serum K > 3 meq/L:
100-200 meq required per each change in serum K of 1 meq/L

If serum K < 3 meq/L:
200-400 meq required per each change in serum K of 1 meq/L

Example: Serum K = 2.5  How much K is required to correct serum K to 4.0?

Step 1
To increase from 2.5 to 3.0: 200-400 meq X 0.5 = 100-200 meq

Step 2
To increase from 3.0 to 4.0: 100-200 meq X 1.0 = 100-200 meq

Total = 200-400 meq
Correct the cause

Oral or IV administration of potassium

Salt substitutes containing $K^+$

Foods high in potassium: bananas, pears, dried apricots; fruit juices; tea, cola beverages; milk; meat, fish; baked potato; dried beans (cooked);
Hypokalemia: Treatment

<table>
<thead>
<tr>
<th>Serum K</th>
<th>Max Infusion Rate</th>
<th>Max. Conc.</th>
<th>Max. Dose 24 hrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 2.5 meq/L</td>
<td>10 meq/hr</td>
<td>40 meq/L</td>
<td>200 meq</td>
</tr>
<tr>
<td>&lt; 2 meq/L</td>
<td>40 meq/hr</td>
<td>60-80 meq/L</td>
<td>400 meq</td>
</tr>
</tbody>
</table>
Hypokalemia: Treatment

- A solution that is too concentrated or a rate of infusion that is too rapid would likely cause phlebitis
- Vehicle?
- Glucose solutions should be avoided as the vehicle because glucose induced insulin secretion will promote intracellular potassium uptake
Mrs D. is a 62 year-old female who is having an acute exacerbation of Crohn’s disease. She complains to you of severe and frequent diarrhea over the last four days. She experiences dizziness when she stands. Your physical examination reveals dry mucous membranes. In the supine position her BP=110/65, pulse=110 and in the upright position her BP=90/45 and her pulse=140. Your lab values are as follows:

Na 132, K 2.9, Cl 92, CO₂ 31, BUN 25, Cr 1.0

Discuss Mrs. D’s fluid and electrolyte problems.
Mrs D’s has *extracellular volume depletion* due to prolonged diarrhea.

The ECVD is supported by her physical assessment and postural hypotension and her BUN/Cr is > 20:1.

The diarrhea has resulted in a loss of fluid and sodium chloride.

Some potassium was lost directly in the stools.

Administration of N/S with Potassium Chloride will correct her fluid and electrolyte problems.
1. Decreased Renal Excretion

   CRF and ARF

   Drug induced:

   K-sparing diuretics (spironolactone, triamterine, amiloride)

   ACEIs
Hyperkalemia: Causes

2. Redistribution
   - Trauma, burns
   - Acidosis

3. Increased intake
   - Salt substitutes
   - Blood transfusions
   - K salts of antibiotics
Metabolic Acidosis and Hyperkalemia

Intracellular Fluid

K+

 Extracellular Fluid 

H+
Hyperkalemia

- ECG shows tall, peaked T waves & dysrhythmias
- Beware of pseudohyperkalemia due to prolonged tourniquet, hemolysis of blood, sampling above KCl infusion
Hyperkalemia: Treatment

1. Potassium Antagonist
   Calcium gluconate

2. Redistribution
   a. Insulin + dextrose
   b. Sodium bicarbonate
   c. Albuterol

3. Cationic binding resins
   Kayexalate (polystyrene sulfonate 1g of resin binds 0.5-1mEq K in exchange with Na)

4. Renal Elimination/dialysis