Pathophysiology

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Lecture 6

II. Disorders of Fluid, Electrolyte, and Acid-Base Balance

Learning Objectives

Upon completing this Lecture the students should be able to:
1. Comprehend the Pathophysiology of SIADH.
2. Comprehend Diabetes Insipidus.
2. Discuss the buffering systems of the body..
3. Know the Pathophysiology of Metabolic acidosis & alkalosis.

V. Syndrome of inappropriate antidiuretic hormone secretion (SIADH)

An abnormal condition characterized by the ***excessive release of antidiuretic hormone (ADH)*** that alters the body's fluid and electrolytic balances.

It results in various malfunctions:

1- **The inability to produce and secrete dilute urine**.
2- **Water retention**.
3- **Increased extracellular fluid volume**.
4- **Hyponatremia**.

SIADH develops **in association with** diseases that affect the **osmoreceptors of the hypothalamus**.

Pathophysiology

1- The release of **ADH is not inhibited** by a reduction in plasma osmolality.
2- Water intake causes **a drop in the plasma osmolality**.
3- Hypo-osmolar state is usually detected as a **low sodium** level on laboratory testing.
4- **Dilutional hyponatremia** is the reason for all the symptoms

SIADH is therefore primarily **a condition that results in the abnormal handling of water loading and not a problem with excessive solute loss.**

This is why it is usually treated with fluid restriction.

Diuretics (furosemide specifically) may also be given to decrease reabsorption of water, with caution.

Causes of SIADH

1 **Malignancy: e.g.** Small cell lung cancer, Sarcoma, Lymphoma, Pancreatic malignancy.
2-**Drugs**

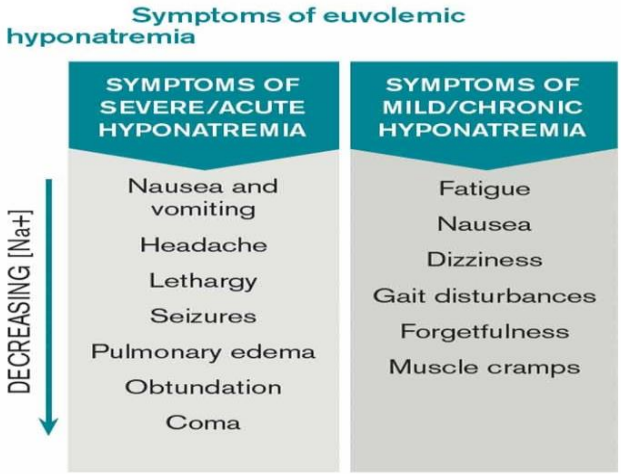
a) Desmopressin
b) Selective serotonin reuptake inhibitors
c) Carbamazepine
d) Prostaglandins
e) Tricyclic antidepressants
f) Phenothiazines
g) Haloperidol
h) 3,4-Methylenedioxymethamphetamine
i) Quinolones
j) Leveteiracetam
k) Cyclophosphamide
l) Vincristine

3- **Intracranial**

a) Tumor
b) Meningitis, Encephalitis, Abscess
c) Traumatic brain injury
d) Subarachnoid hemorrhage, Subdural hemorrhage

Clinical manifestations are :

1. Oliguria.
2. Oedema.
3. Those of **Euvolemic hyponatremia** and the underlying disease.



VI. Diabetes Insipidus

Diabetes insipidus (DI) is a disorder that causes the patient to produce tremendous quantities of urine. The massively increased urine output is usually accompanied by intense thirst.

It resulting from:

1- *A deficiency of vasopressin ADH.*

2- Renal not responding to the ADH.

Classification of Diabetes insipidus

1- **Neurogenic** diabetes insipidus: Decrease or insufficient production of ADH
2- **Nephrogenic** diabetes insipidus: Inability of the kidney to respond normally to vasopressin.
3- **Dipsogenic**: **Damage to the thirst mechanism**, which is located in the hypothalamus resulting in increase in thirst and fluid intake that suppresses vasopressin secretion and increases urine output.
4- **Gestational diabetes insipidus**: Occurs during pregnancy due to produce ***vasopressinase*** **from the placenta**, which breaks down ADH.
5- Familial disease: (**X-linked**), (**autosomal-recessive**)
6- **Idiopathic**: unknown etiology.

Acid-Base Balance DISORDERS

Buffer:

Is a solution of two or more chemical compounds that prevent marked changes in H^+ ion concentration when either an acid or base is added to solution.

Buffer systems do not prevent pH change but rather minimize the pH change.

Buffer systems

1. Plasma.
2. RBC.
3. Urine.

Acid production

Acids are produced through body metabolism or ingested. They **cannot be excreted as a gas** through the lungs. Must be excreted in a liquid form through **the kidney**.

1. **Catabolism of Protein**
   a) Amino acids.
   b) Uric acid.
   c) Sulfuric acid.
   d) Phosphoric acid.
2. **Catabolism of Carbohydrates**
   a) Pyruvic acid.
   b) Succinic acid.
   c) Lactic Acid (if no oxygen is present).
3. **Catabolism of Lipids**
   a) Fatty acids.
   b) Ketoacids (if no insulin is present):
      - Acetoacetic acid.
      - Beta-hydroxybutyric acid.

The only volatile acid is carbonic acid (H_2CO_3). This acid is in equilibrium with its dissolved gaseous component ($PaCO_2$).

Anion gap:

R*epresents the concentration of all the unmeasured anions in the plasma.*

*The **negatively charged proteins account for about 10%** of plasma anions and make up the majority of the **unmeasured anion** represented by the anion gap under normal circumstances).*

AG is calculated from the following formula:

Anion gap = $[Na^+]$ - $[Cl^-]$ - $[HCO3^-]$

Reference range is 8 to 16 mmol/l.

The pH is not only determined by the [H+] and [HCO3-], other ions in solution influence pH.

There are dependent and independent variables determining pH

Dependent

1) **H+**
2) **OH-**
3) **HCO3-**
4) **CO32-**
5) **HA (weak acid)**
6) **A- (weak ions)**

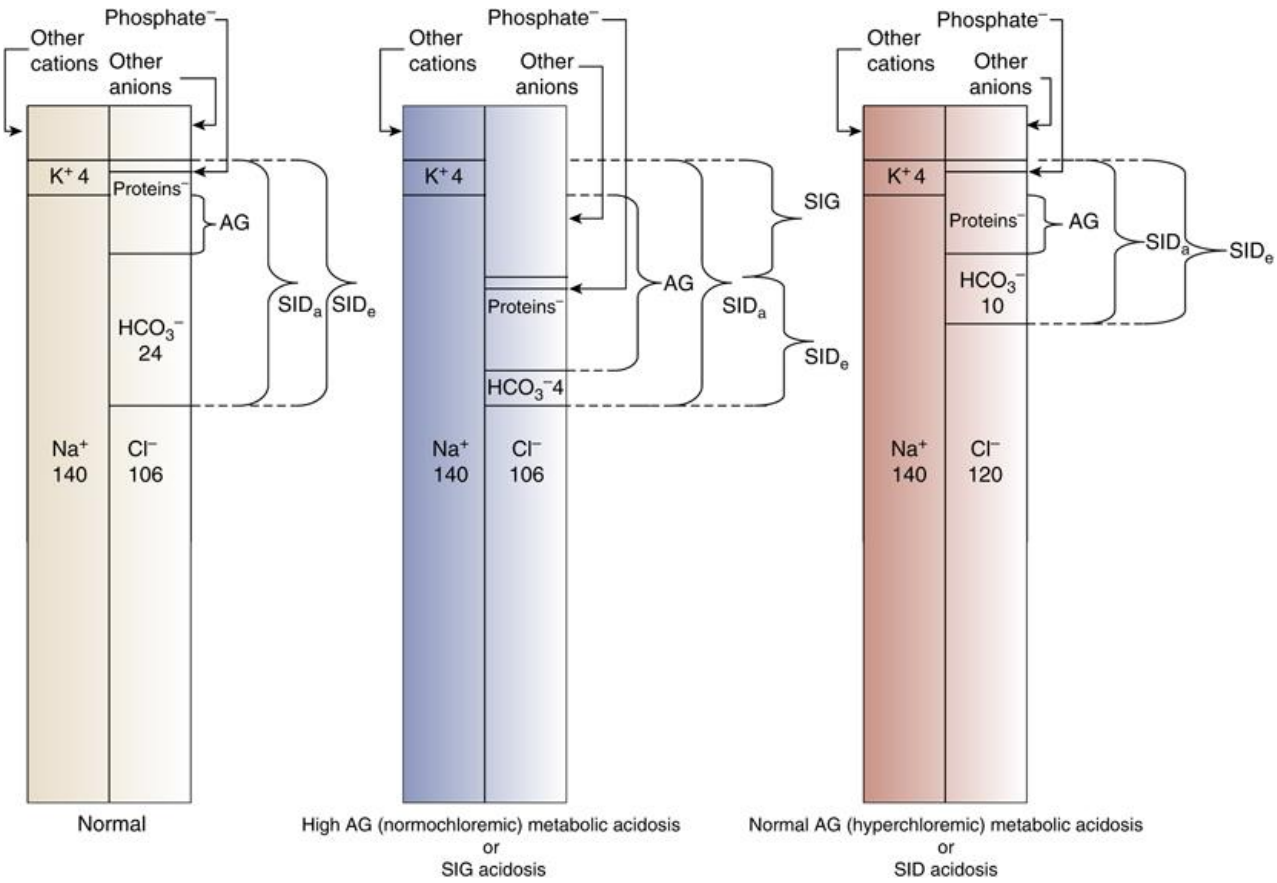
Independent

1) **P_{CO2}**
2) **ATOT (total weak non-volatile acids)** *is an acid produced in the body from sources other than carbon dioxide, and is not excreted by the lungs*
3) **SID (net Strong Ion Difference)** ***Strong ions are cations and anions that exist as charged particles dissociated from their partner ions at physiologic pH. ... The Strong Ion Difference (SID) is the difference between the positively- and negatively-charged strong ions in plasma.***

Strong ions are those ion that dissociate totally at the pH of interest in a particular solution.
In blood at pH 7.4:
Strong cations are: Na^+, K^+, Ca^{2+}, Mg^{2+}.
Strong anions are: Cl^- and SO_4^{2-}.

The number of positive and negative ions in a solution must be equal (SID = 0)

1) **Increased SID (>0) leads to alkalosis (increase in unmeasured anions).**
2) **Decreased SID (<0) acidosis.**



SIG acidosis= Strong Ion Gap Acidosis.
SID acidosis= Strong Ion Difference Acidosis.

(Note):

a) Loss of buffer has no effect on anion gap.
b) Accumulation of organic acid (e.g., lactic acid) causes an increase in anion gap.

Major Clinical Uses of the Anion Gap

1. **To signal the presence of a metabolic acidosis** and confirm other findings
2. **Help differentiate** between causes of a metabolic acidosis**: high anion gap** versus **normal anion gap metabolic acidosis**.

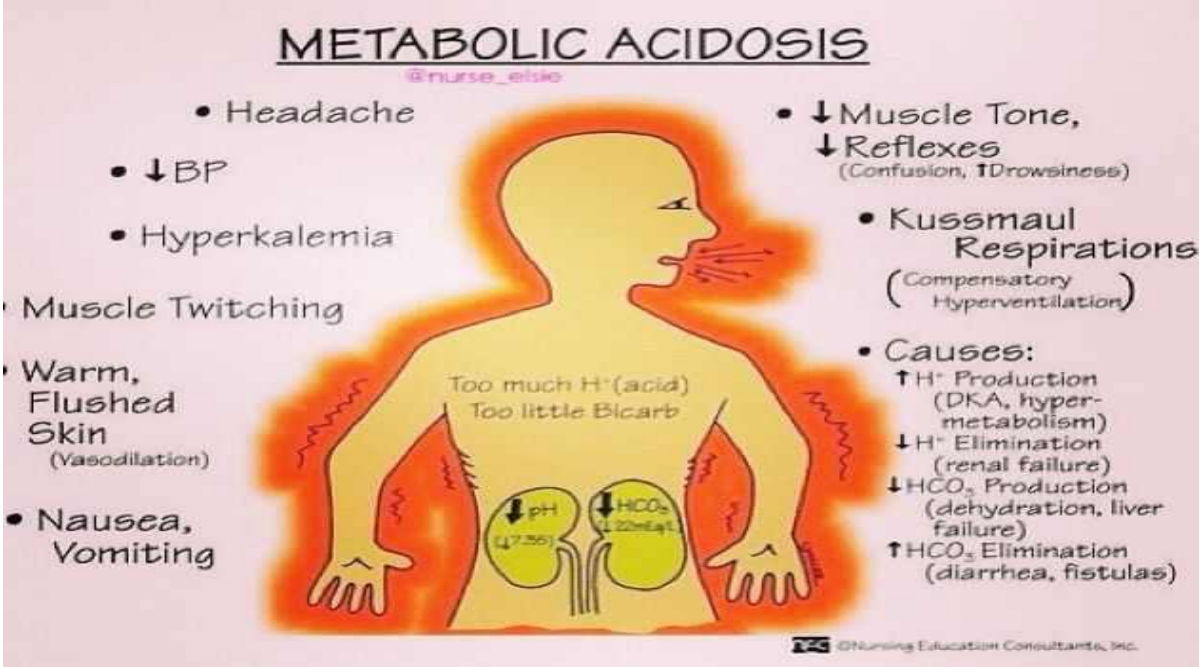
   In **an inorganic metabolic acidosis** (eg due HCl infusion), the infused Cl^- replaces HCO_3 and the anion gap remains **normal**.

   In **an organic acidosis**, the lost bicarbonate is replaced by the acid anion which is not normally measured. This means that the **AG is increased**.
3. To **assist the biochemical severity** of the acidosis and follow the response to treatment.

VII. Metabolic acidosis

Metabolic acidosis is defined as:

1) **An arterial blood pH <7.35**
2) **With plasma bicarbonate <22 mmol/L.**



Metabolic acidosis occurs when:

1. **The body produces too much acid**.
2. **When the kidneys are not removing enough acid from the body.**

There are several types of metabolic acidosis. The main causes are best grouped by their influence on the **anion gap.**

Common causes of metabolic acidosis:

1. **Bicarbonate loss**, especially via immature kidney or from GI tract.
2. **Lactic acidosis** from inadequate tissue perfusion and oxygenation (e.g., from asphyxia, shock, severe anemia, hypoxemia, Potent Ductus Arteriosus, excessive ventilator pressures with ↓ cardiac output).
3. **Hypothermia.**
4. **Excessive Cl** in IV fluids.
5. **Renal failure.**
6. **Excessive acid** Diabetic ketoacidosis, Alcoholic ketoacidosis, Salicylate intoxication
7. **Excretion of $HCO3^-$** as metabolic compensation for respiratory alkalosis
8. **Drugs** such as (spironolactone, prostaglandin inhibitors, triamterene, amiloride, trimethoprim, pentamidine, ciclosporin).
9. Severe **Diarrhea**.

Dilution acidosis

Is caused by **excessive volume expansion** (with saline, Ringer's lactate or dextrose solutions). The extracellular space becomes "diluted" (relative decrease of $HCO3^-$); carbonic acid dissociates more and liberates more H^+. **Therefore, pH falls**.

Effects of metabolic acidosis:

Major physiological effects of metabolic acidosis include:

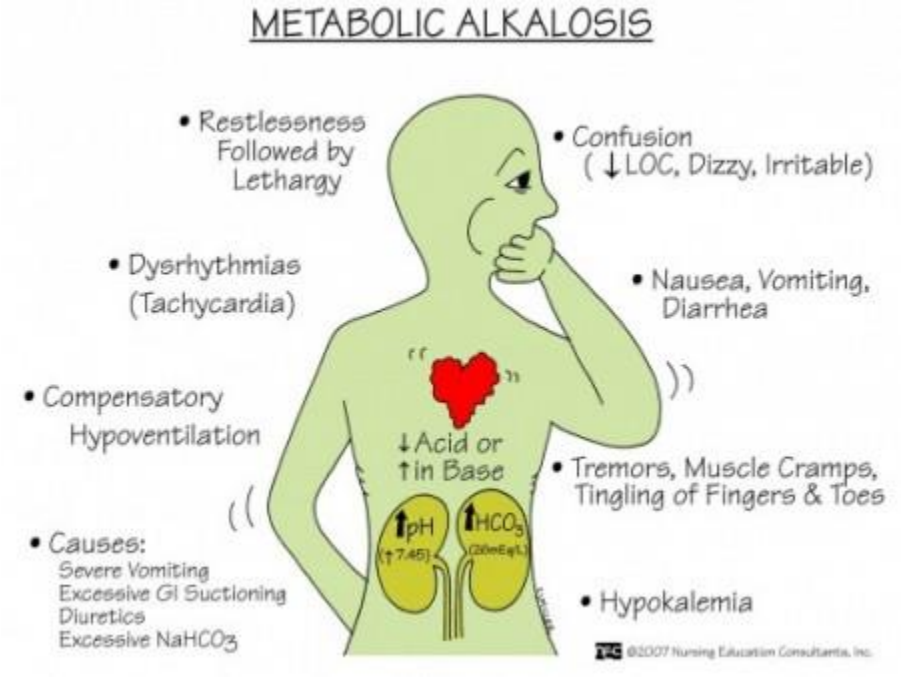
1. **Pulmonary vasoconstriction** (with risk of persistent pulmonary hypertension)
2. **Decreased myocardial contractility**
3. **Shift of O_2-Hgb dissociation curve to right** (Decreased saturation at a given PO_2)
4. **CNS damage** with severe acidosis.
5. **An increase in respiratory** as compensation for acidosis. **Tachypnea.**

VIII. METABOLIC ALKALOSIS

Metabolic alkalosis refers to a condition that leads to a **primary increase in serum bicarbonate concentration** ([$HCO3^-$]).

Occurring as a consequence of :

1. **A gain in $HCO3^-$** .
2. **A loss of H^+** from the body.



Causes

1. **Eucapnic ventilation** Post- Hypercapnia (**Increase CO_2**).
2. **Loss of gastric fluid**. (**Loss of HCL**).
3. **Thiazide or loop diuretics**. (**Contraction Alkalosis**).
4. **Non-absorbable antacids**.
5. **Alkaline ingestion**.

There are other causes but these are the main.

Pathophysiology

Metabolic alkalosis manifests as **alkalemia (pH >7.40)**.

1- Compensatory phase:

As compensatory mechanism, Metabolic alkalosis yields to **alveolar hypoventilation** with the consequent **increase in arterial carbon dioxide tension** ($PaCO_2$). This compensatory rise in $PaCO_2$, minimize the change in pH.

Arterial $PaCO_2$ quickly increases by roughly 0.7 mmHg for every 1 mmol/L increase in plasma [HCO_3^-]. Mostly a complex or mixed acid-base disturbance occurs when the change in $PaCO_2$ is not within the expected range.

A $PaCO_2$ that increases more than 0.7 times the rise in bicarbonate indicates the coexistence of Metabolic alkalosis with primary respiratory acidosis.

2- The maintenance phase: of metabolic alkalosis is

a. **Accelerated H^+ secretion** that allows increased bicarbonate reabsorption.

b. Resulting in a **paradoxical aciduria**.

Sometimes a **distinct generation phase raises the HCO_3^- initially**. Increased HCO_3^- reabsorption by the kidney can be caused by one of two distinct categories of disorders: Cl^- responsive and Cl^- resistant.

Clinical manifestations

In critically ill patients, = significant increase in morbidity and mortality

1. **Decreased myocardial contractility.**
2. **Arrhythmias.**
3. **Decreased cerebral blood flow (vasoconstriction).**
4. **Neuromuscular excitability → tetany → difficult ventilation.**
5. **Confusion, seizures.**
6. **Hypoventilation, thus atelectasis**.

Thank you