Inorganic Pharmaceutical Chemistry

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Replacement Therapy

Replacement Therapy

- The basic objective of replacement therapy is to restore **the volume** and **composition** of the body fluids to normal one.
- Volume contraction is a **life threatening** condition because:

1. It impairs the circulation.
2. Blood volume decreases.
3. Cardiac output falls

1- Sodium Replacement

- **Hypotonic solutions** are administered for maintenance therapy when patients are unable to take fluids and nutrients orally for one to three days.
- **Hypertonic injections** are used when there is loss of sodium in excess (should be given slowly in small volume 200-400ml).

- **Official Preparations of Sodium Replacement:**

1. Sodium Chloride Injection, solution & tablets.
2. Bacteriostatic sodium chloride injection.
3. Dextrose and sodium chloride injection & tablets.
4. Mannitol and sodium chloride injection.
5. Fructose and sodium chloride injection.
6. Ringer's injection.
7. Lactate ringer's injection.

2- Potassium Replacement

- Used in:

1. **Oral replacement** of potassium (Irritating to GIT & sol. Must be well diluted).
2. **Familial periodic paralysis** (a recurring, rapidly progressive, flaccid paralysis).
3. **Meniere's syndrome** (disease of inner ear which includes dizziness and noise in the ear).
4. **As antidote in digitalis intoxication** (not a specific antidote and can potentiate some of the cardiac complication).
5. **As an adjunct to drugs used in the treatment of myasthenia gravis** (A progressive, sever muscle weakness).

2- Potassium Replacement

➢ **Contraindication** in patient with:

1. Impaired renal function with **oliguria** (diminished urine output).
2. Acute dehydration.
3. Hyperpotassemic condition such as **myotonia congenita** (tonic muscle rigidity & spasm).
4. Potassim-sparing **drugs.**

2- Potassium Replacement

- Official Preparations of Potassim Replacement:

1. Potassium Chloride injection & tablets.
2. Ringer's injection.
3. Lactate Ringer's injection.
4. Lactate potassium saline injection.
5. Potassium gluconate elixir & tablets.

3- Calcium Replacement

- **Used as:** the calcium **source** in many commercially available electrolyte replacement and maintenance solutions.
- Official **Preparations** of Calcium Replacement:

1. Calcium chloride include: **Ringer's** injection & **Lactate ringer's** injection.
2. Calcium gluconate injection & tablets.
3. Calcium lactate tablets.
4. Dibasic calcium phosphate.
5. **Tribasic** calcium phosphate.

4- Parenteral Magnesium Administration:

- When injected has been used as central nervous system depressant in the treatment of eclampsia (convulsions and coma), and in magnesium deficient alcoholics.
- Overtreatment can cause respiratory paralysis and cardiac depression.
- I.V. injection of Ca salts is used to counteract Mg intoxication.
- Should not be administered in patient with renal insufficiency.

- **Used as**:

1. Anticonvulsant.
2. Cathartic.

- Official Preparations of Magnesium: **Magnesium sulfate injection**

Electrolyte combination therapy:

- **Combination** of **glucose and saline** solution sufficient in **short term** therapy for restoring electrolytes loss.
- But in **sever deficiency** of electrolyte due to heavy blood loss or chronic diarrhea, solution containing **additional** electrolytes are usually required
- The combination product of tow types :

1. **Fluid maintenance therapy**
2. **Electrolyte's replacement therapy**

1. **Maintenance therapy:** with I.V. is required to supply normal necessity of water and electrolytes to patient who cannot take them orally

- All maintenance therapy should contain at least 5% dextrose

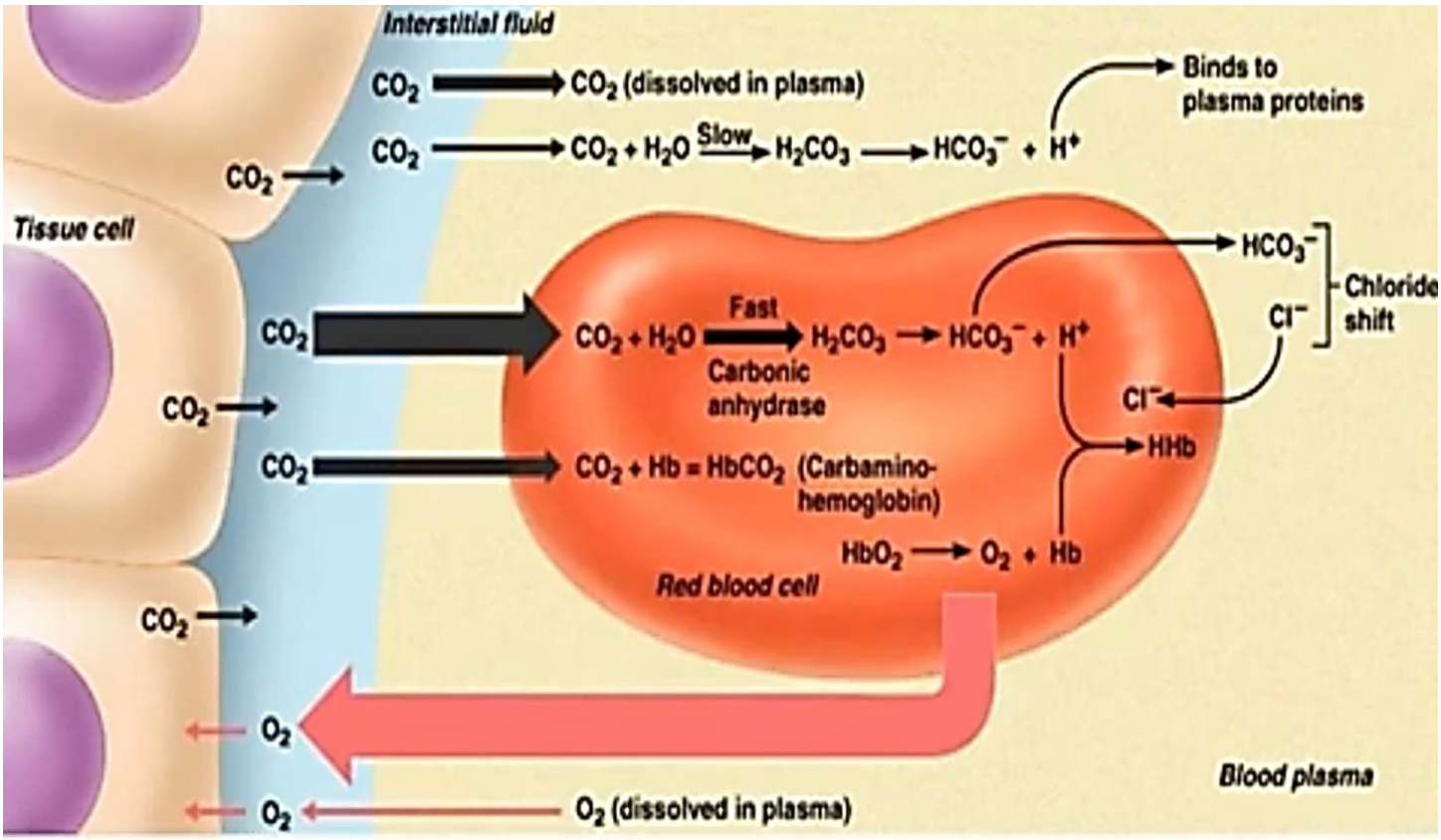
2. **Replacement therapy:** is required when there is **excess loss** of water and electrolytes caused by fever, sever vomiting and diarrhea.

Physiological Acid Base Balance

- Disturbances of the **pH** of body are frequently **encounter** and are of major clinical importance.
- **Acedemia** and **alkalemia** refer respectively to an abnormal **decrease** or **increase** in the pH of the blood.
- **Acidosis** and **alkalosis** refer respectively to clinical state that can lead to either acedemia or alkalemia.
- Acids either **carbonic** from **carbon dioxide** or **lactic** from anaerobic metabolism) are constantly being produced during metabolism.
- Most metabolic reactions occur only within narrow pH range of **7.38-7.42,** therefore the body utilizes several efficient **buffer systems.**

- **Two** of the major buffer system in the body are **bicarbonate/carbonic acid** **(HCO_3^-/H_2CO_3)** found in the plasma & kidney and **monohydrogen phosphate/dihydrogen phosphate** **($HPO_4^{-2}/H_2PO_4^-$)** found in the cells and kidneys.
- **Carbon dioxide** diffuses from the **cell** into the **plasma** where a small portion **dissolved** and another small portion **reacts** with **water** to form **carbonic acid**.
- The **increased carbonic acid** is buffered by plasma proteins.
- **Most** CO_2 enters the **erythrocytes** where it either rapidly forms H_2CO_3 by the action of **carbonic anhydrase** or **combines** with **Hb**.
- The tendency to **lower** the pH of the erythrocytes **due to** increased concentration of H_2CO_3.

- The **bicarbonate anion** then **diffuses out** of **erythrocytes** and **chloride anion** **diffuses in**.
- This has been named as **chloride shift**.
- The **bicarbonate** in plasma, along with the plasma **carbonic acid** now acts as **efficient buffer** system.
- The normal **HCO_3^-/ H_2CO_3** ratio is 27/1.35 meq/l (20:1) corresponding to pH 7.4.

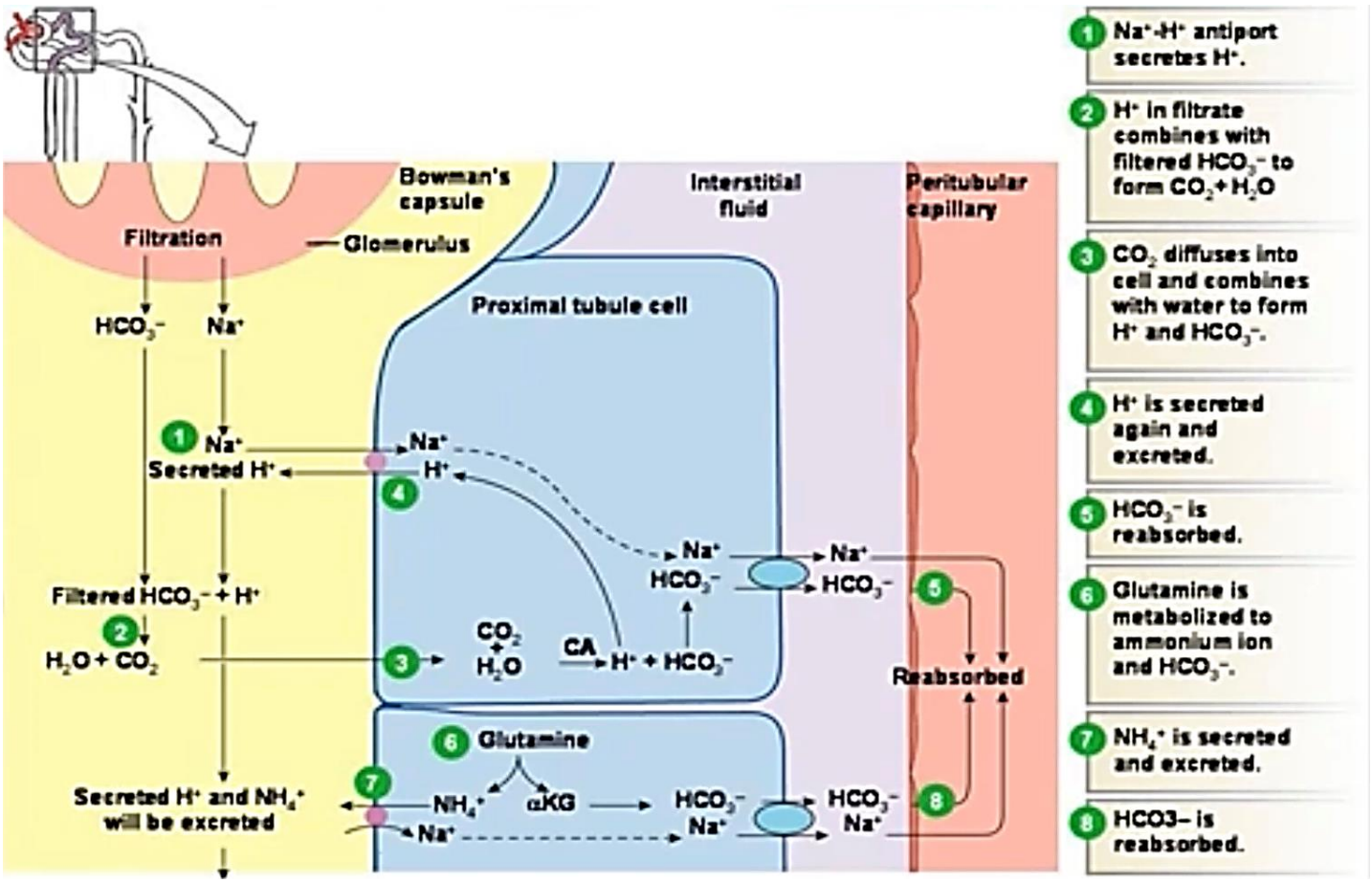


a) Oxygen release and carbon dioxide pickup at the tissues

- In **lungs** there is reversal of the above process due to the large amount of O_2 present.
- **Oxygen** **combines** with the protonated **deoxyhemoglobin** **releasing** **proton**.
- **These** combine with **$HCO3^-$** forming **H_2CO_3** which then **dissociates** to CO_2 and water.
- The **carbon dioxide** is **exhaled** by the lungs.
- Thus by regulating breathing it is possible for the body to exert a partial control on the HCO_3^- /H_2CO_3 ratio.

- The **phosphate buffer system** is also effective in maintaining physiological P^H.
- At **pH 7.4** the **$HPO_4^{-2}/H_2PO_4^{-1}$** ratio is approximately 4:1. In kidney, the pH of urine can **drop** to **4.5-4.8** corresponding to $HPO_4^{-2}/H_2PO_4^{-}$ ratio of 1:99 - 1:100.
- The **steps of acid excretion from kidney** shown as following:

- **Sodium salt** of mineral or organic acids are **removed** from the plasma by **glomerular filtration**.
- Sodium is preferentially **removed** from the renal filtrate or tubular fluid and in the tubular cells **reacts** with **carbonic acid** formed by the ***carbonic anhydrase*** .
- The **$NaHCO_3$** returns to the plasma (eventually being removed in the lungs as CO_2) & the **protons** enter the tubular fluid, **forming** acids of the anions that originally were sodium.


Bowman's capsule
Interstitial fluid
Peritubular capillary
Filtration
Glomerulus
Proximal tubule cell
HCO_3^-
Na^+
1 Na^+
Secreted H^+
Na^+
H^+
4
Na^+
HCO_3^-
Na^+
HCO_3^-
5
Filtered $HCO_3^- + H^+$
2
$H_2O + CO_2$
3
CO_2 + H_2O
CA
$H^+ + HCO_3^-$
Reabsorbed
6 Glutamine
7
Secreted H^+ and NH_4^+ will be excreted
NH_4^+
αKG
HCO_3^-
Na^+
HCO_3^-
Na^+
8
1 Na^+-H^+ antiport secretes H^+.
2 H^+ in filtrate combines with filtered HCO_3^- to form $CO_2 + H_2O$
3 CO_2 diffuses into cell and combines with water to form H^+ and HCO_3^-.
4 H^+ is secreted again and excreted.
5 HCO_3^- is reabsorbed.
6 Glutamine is metabolized to ammonium ion and HCO_3^-.
7 NH_4^+ is secreted and excreted.
8 HCO3– is reabsorbed.

➢ Types and Causes of Acidosis:

A. Metabolic acidosis: primary **bicarbonate ion deficit**, (diabetic acidosis, renal failure and diarrhea).

- **Buffer System**: HCO_3^-/H_2CO_3. Compensatory
- **mechanisms:** Hyperventilation causing increased excretion of H_2CO_3 as CO_2 (respiratory function), increased acid excretion by Na^+-H^+ exchange, increased NH_3 formation and HCO_3^- reabsorption (renal function).

A. Respiratory Acidosis: primary **carbonic acid excess** (cardiac disease, lung damage, drowning).

- **Buffer system**: hemoglobin and protein. Compensatory
- **mechanisms:** increased CO_2 excretion through the lungs (respiratory function), increased acid excretion by Na^+-H^+ exchange, increased NH_3 formation and HCO_3^- reabsorption (renal function).

➢ Types and Causes of Alkalosis:

A. Metabolic alkalosis: primary **HCO_3^{-1}** **excess** (administration of excess alkali, vomiting, potassium ion).

- **Buffer System:** HCO_3^-/H_2CO_3. Compensatory
- **mechanisms:** CO_2 retention causing increased H_2CO_3 concentration (respiratory function), decreased Na^+-H^+ exchange, decreased NH_3 formation , and reabsorption of HCO_3^- (renal function).

B. Respiratory alkalosis: primary **H_2CO_3** **deficit**, (fever, hysteria, anoxia, salicylate poisoning).

- **Buffer System**: HCO_3^-/H_2CO_3. Compensatory
- **mechanisms**: CO_2 retention causing increased H_2CO_3 concentration (respiratory function), decreased Na^+-H^+ exchange, decreased NH_3 formation, and reabsorption of HCO_3^- (renal function).

Electrolytes used in acid base balance:

1. Sodium acetate

which is metabolized to carbon dioxide and then to bicarbonate, can be used as an effective buffer in metabolic acidosis.

It approaches sodium bicarbonate in its ability to restore blood pH and plasma bicarbonate in patient suffering from:

1) **Metabolic acidosis of acute cholera (a disease involving severe diarrhea resulting in the loss of electrolytes).**
2) **Uremic acidosis (acidic urine).**

2. Potassium acetate

It categorized as an alkalizer. Along with potassium citrate and bicarbonate, it is found in potassium triplex.

3. Sodium bicarbonate

Sodium bicarbonate used to:

1) **Combate gastric hyperacidity.**
2) **To combate systemic acidosis.**
3) **For miscellaneous uses.**

Found as sodium bicarbonate injection and tablets.

4. Potassium bicarbonate

It is officially classified as an electrolyte replenisher

5. Sodium biphosphate

It is classified as urinary acidifier.

6. Sodium citrate

Sodium citrate is official for its use as an anticoagulant for whole blood, it chelates serum calcium, thereby removing one of the components of blood clotting. Citrates are used for the chelation of other cations. Citric acid and its salts are also used as buffering agents. Because citrate, a component of the Krebs cycle, is rapidly metabolized to carbon dioxide and then to bicarbonate, sodium citrate is used in chronic acidosis to restore bicarbonate reserve. It also has a diuretic effect due to increased body salt concentration. The kidney excretes this extra salt.

Found as: anticoagulant citrate dextrose solution, anticoagulant citrate phosphate dextrose solution.

7. Potassium Citrate

It is classified as an alkalizer. It is a component of Triplex along with potassium acetate and bicarbonate.

8.Sodium Lactate

It is commercially available as a mixture with water containing 70-80% sodium lactate. Although the lactate obtained during anaerobic glycolysis has the L-configuration, the commercial preparation are mostly racemic mixtures. Sodium lactate is official as Sodium Lactate Injection. It is used as a fluid and electrolyte replenisher for treatment of metabolic acidosis.

9.Ammonium Chloride

The ammonium cation falls into certain pharmacological categories:

1) **Acid-base equilibrium of the body.**
2) **Diuretic effect.**
3) **Expectorant effect.**

Electrolyte Combination Therapy

A.Infusions:

In short-term therapy, such as following surgery, infusion of standard glucose & saline solution may be adequate. While combinations compounded according to need of each individual patient would be ideal. These combination products can be divided into two groups: fluid maintenance and electrolyte replacement. Maintenance therapy with intravenous fluids is intended to supply normal requirements for water and electrolytes to patients who cannot take them orally. All maintenance solutions should contain at least 5% dextrose. In addition to dextrose, the general electrolyte composition of maintenance solutions is Na, K, Cl, HCO3 (or equivalent amounts of lactate or acetate), Mg, and P.

Replacement therapy is needed as in:

1) **Prolonged fever.**
2) **Severe vomiting.**
3) **Diarrhea.**

There are two types of solutions used in replacement therapy:

1) **Solution for rapid initial replacement.**
2) **Solution for subsequent replacement.**

The electrolyte concentrations in solution for rapid initial replacement more or less resemble the electrolyte concentrations found in ECF. Some may have larger amounts of potassium, the concentration of ions varies, these variations allows the clinician to select solution which best fits the electrolyte and acid-base needs of the patients

Official combination of electrolyte infusions:

1) **Ringer's injection**

It contains potassium Chloride, sodium chloride, and calcium chloride (as the dihydrate). This is equivalent to Na, K, Ca, and Cl.

2) **Lactated Ringer's Injection**

It contains sodium chloride, sodium lactate, potassium chloride and calcium chloride (as the dihydrate). These are equivalent to Na, K, Ca, Cl and lactate. It is usually available as injections.

B.Oral Electrolyte Solutions

Orally administered electrolyte solutions are available. used to supply water and electrolytes in amounts needed for maintenance as soon as intake of usual foods and liquids is discontinued and serious fluid losses or deficits occur (diarrhea, etc.). These solutions are not intended to promote the total water requirements of the individual. If additional liquid is needed, water or other nonelectrolyte fluids should be given. There have been sodium chloride, and sodium chloride plus dextrose tablets available for years to replace the salt lost through excessive perspiration.