**DIURETICS**

Diuretics are drugs that promote the output of urine excreted by the Kidneys. The primary action of most diuretics is the direct inhibition of $\text{Na}^+$ transport at one or more of the four major anatomical sites along the nephron, where $\text{Na}^+$ reabsorption takes place. The increased excretion of water and electrolytes by the kidneys is dependent on three different processes viz., glomerular filtration, tubular reabsorption (active and passive) and tubular secretion.

Diuretics are very effective in the treatment of Cardiac oedema, specifically the one related with congestive heart failure. They are employed extensively in various types of disorders, for example, nephritic syndrome, diabetes insipidus, nutritional oedema, cirrhosis of the liver, hypertension, oedema of pregnancy and also to lower intraocular and cerebrospinal fluid pressure.

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**Therapeutic Uses of Diuretics**

i) Congestive Heart Failure: The choice of the diuretic would depend on the severity of the disorder. In an emergency like acute pulmonary oedema, intravenous Furosemide or Sodium ethacrynate may be given. In less severe cases, Hydrochlorothiazide or Chlorthalidone may be used. Potassium-sparing diuretics like Spironolactone or Triamterene may be added to thiazide therapy.

ii) Essential hypertension: The thiazides usually sever as primary antihypertensive agents. They may be used as sole agents in patients with mild hypertension or combined with other antihypertensives in more severe cases.
iii) Hepatic cirrhosis: Potassium-sparing diuretics like Spironolactone may be employed. If Spironolactone alone fails, then a thiazide diuretic can be added cautiously. Furosemide or Ethacrynic acid may have to be used if the oedema is refractory, together with spironolactone to lessen potassium loss. Serum potassium levels should be monitored periodically.

iv) Nephroic syndrome: Dietary sodium restriction may be combined with a thiazide diuretic, adding Spironolactone to control secondary hyperaldosteronism

CLASSIFICATION

Diuretics may be classified as follows.


ii) Carbonic – Anhydrase inhibitors: eg. Acetazolamide, Methazolamide, Ethoxzolamide, Diclofenamide, Disulfamide.

iii) Sulphonamide diuretics: eg. Quinethazone, Chlortalidone, Metolozone, Indapamide, Clopamide, Xipamide.


vi) Loop (or) High – ceiling diuretics: eg. Burmetanide, Furosemide, Ethacrynic acid.


viii) Miscellaneous diuretics: eg. Triamterene, Muzolimine.

2.1. THIAZIDE AND HYDROTHIAZIDE DIURETICS

Thiazides are having the following general chemical formula.
Thiazide and Hydrothiazide Diuretics

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>R</th>
<th>R₁</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorthiazide</td>
<td>- Cl</td>
<td>- H</td>
</tr>
<tr>
<td>Benzthiazide</td>
<td>- Cl</td>
<td>- CH₂ - S - CH₂</td>
</tr>
</tbody>
</table>

Hydrochlorthiazide (Hydride, Thiazide)

Carbonic anhydrase inhibitors are derived from sulphonamide antibacterial. Acetazolamide is the proto-type carbonic anhydrase inhibitor.

This type of diuretics inhibit carbonic anhydrase enzyme in the membrane and cytoplasm of the epithelial cell. Carbonic anhydrase influence tubular reabsorption of sodium at two sites: in the proximal tubule where bicarbonate absorption occurs and in the distal tubule where sodium is exchanged for potassium or hydrogen ion and bicarbonate is formed as an accompanying anion.

The hydration of CO₂ takes place under the influence of carbonic anhydrase to form carbonic acid which dissociates to give hydrogen and bicarbonate ion.
Carbonic anhydrase helps to produce H\(^+\) ion, which are secreted into the tubules in exchange for Na\(^+\) ion. The sodium-hydrogen ion exchange takes place almost all along the length of the renal tubule and normally is responsible for the formation of acid urine, while conserving the stores of bicarbonate along with sodium.

Carbonic anhydrase inhibitors act by blocking the enzyme, while prevents the reabsorption of HCO\(_3^-\). Accumulation of HCO\(_3^-\) in the tubules inhibits Na\(^+\) - H\(^+\) exchange and Na\(^+\) reabsorption.

The sodium is eliminated along with bicarbonate ions and the water in which they are dissolved. The urine becomes alkaline the increase in Na\(^+\) concentration in the tubular fluid may be compensated partially by increased NaCl reabsorption in later segment of the tubule. Thus the diuretic effect of the carbonic anhydrase inhibitors in mild.

These agents decrease the activity of carbonic anhydrase at other sites in the body like the CNS, the eye, the lungs and the gastrointestinal tract.

**Acetazolamide (Acetamide, Avva)**

\[
\begin{align*}
N & - (5 - Sulfamoyl - 1,3,4 - thiadiazol - 2 - yl) \text{ acetamide.}
\end{align*}
\]

**SULPHONAMIDE DIURETICS**

The actions of these drugs are very similar to the thiazide diuretics, except that these specifically possess longer duration of action.
ALDOSTERONE ANTAGONISTS

Spiranolate (Aldactone, Aldactide)

![Chemical Structure]

7-(Acetylthio)-17-hydroxy-3-oxopregn-4-en-21-carboxylic acid lactone

ADR: Fluid or electrolyte imbalance, gynaecomestia.

Dose: 25-100mg daily.

Use: It is useful in cirrhosis of liver, aldosterone - secreting tumors and high – renin hypertension.

HIGH CEILING OR LOOP DIURETICS

Furosemide, Bumetanide and Ethacrynic acid have been labelled as “high-ceiling” or loop diuretic”, because they inhibit the sodium and chloride reabsorption in the thick segment of the ascending limb of the loop of Henle as well as in the proximal convoluted tubule and the distal diluting site. Thus they are very potent diuretics, and induce a dramatic and copious flow of urine rich in sodium chloride. The loop diuretics have completely replaced the mercurials (mersaly). The use of organomercurials and ammonium chloride as diuretics is obsolete.

Their major action is to reduce active Cl- reabsorption in the ascending limb of the loop of Henle. In addition, there are minor actions on Na+ reabsorption in the proximal tubule, and the distal tubule. There is an increased urine volume with loss of Na+, K+ and Cl-. The Cl- loss induces hypochloraeic alkalosis and K+ loss may provoke digoxin intoxication. Uric acid secretion is reduced and this may induce gout in susceptible individuals. Unlike most other diuretics, the loop diuretics continue to be effective even in the presence of electrolyte and acid-base imbalance and nitrogen retention.

Furosemide and Bumetanide are sulphonamide compounds. Both of them as well as Ethacrynic acid, contain a free carboxyl group, which helps them to be transported into a longer segment of the tubule than the thiazides. Hence the loop diuretics inhibit sodium and
chloride reabsorption over a longer length of the nephron producing more diuresis than the thiazides