Urinary System Drugs

Urinary system

The urinary system consists of the kidneys, ureters, urinary bladder, and urethra. The kidneys filter the blood to remove wastes and produce urine. The ureters, urinary bladder, and urethra together form the urinary tract, which acts as a plumbing system to drain urine from the kidneys, store it, and then release it during urination. Besides filtering and eliminating wastes from the body, the urinary system also maintains the homeostasis of water, ions, pH, blood pressure, calcium

Kidneys: The kidneys are the waste filtering and disposal system of the body. As much as 1/3 of all blood leaving the heart passes into the kidneys to be filtered before flowing to the rest of the body's tissues. While a person could live with only one functioning kidney, our kidneys are vital organs; the loss of both kidneys would lead to a rapid accumulation of wastes and death within a few days time.

The kidneys are bean-shaped with the convex side of each organ located laterally and the concave side medial. The indentation on the concave side of the kidney, known as the renal hilus, provides a space for the renal artery, renal vein, and ureter to enter the kidney.

Each kidney contains around 1 million individual nephrons, the kidneys' microscopic functional units that filter blood to produce urine. The nephron is made of 2 main parts: the renal corpuscle and the renal tubule.

Responsible for filtering the blood, our renal corpuscle is formed by the capillaries of the glomerulus and the glomerular capsule (also known as Bowman's capsule). The glomerulus is a bundled network of capillaries that increases the surface area of blood in contact the blood vessel walls. Surrounding the glomerulus is the glomerular capsule, a cup-shaped double layer of simple squamous epithelium with a hollow space between the layers. Special epithelial cells known as podocytes form the layer of the glomerular capsule surrounding the capillaries of the glomerulus. Podocytes work with the endothelium of the capillaries to form a thin filter to separate urine from blood passing through the glomerulus. The outer layer of the glomerular capsule holds the urine separated from the blood within the capsule. At the far end of the glomerular capsule, opposite the glomerulus, is the mouth of the renal tubule.

A series of tubes called the renal tubule concentrate urine and recover non-waste solutes from the urine. The renal tubule carries urine from the glomerular capsule to the renal pelvis.

1. The curvy first section of the renal tubule is known as the proximal convoluted tubule. The tubule cells that line the proximal convoluted tubule reabsorb much of the water and nutrients initially filtered into the urine.
2. Urine next passes through the loop of Henle, a long straight tubule that carries urine into the renal medulla before making a hairpin turn and returning to the renal cortex.
3. Following the loop of Henle is the distal convoluted tubule.
4. Finally, urine from the distal convoluted tubules of several nephrons enters the collecting duct, which carries the concentrated urine through the renal medulla and into the renal pelvis.
5. From the renal pelvis urine from many collecting ducts combines and flows out of the kidneys and into the ureters.

Ureters: The ureters are a pair of tubes that carry urine from the kidneys to the urinary bladder. The ureters are about 10 to 12 inches long and run on the left and right sides of the body parallel to the vertebral column. Gravity and peristalsis of smooth muscle tissue in the walls of the ureters move urine toward the urinary bladder. The ends of the ureters extend slightly into the urinary bladder and are sealed at the point of entry to the bladder by the ureterovesical valves. These valves prevent urine from flowing back towards the kidneys.

Urinary Bladder: The urinary bladder is a sac-like hollow organ used for the storage of urine. The urinary bladder is located along the body's midline at the inferior end of the pelvis. Urine entering the urinary bladder from the ureters slowly fills the hollow space of the bladder and stretches its elastic walls. The walls of the bladder allow it to stretch to hold anywhere from 600 to 800 milliliters of urine.

Urethra: The urethra is the tube through which urine passes from the bladder to the exterior of the body. The female urethra is around 2 inches long and ends inferior to the clitoris and superior to the vaginal opening. In males, the urethra is around 8 to 10 inches long and ends at the tip of the penis. The urethra is also an organ of the male reproductive system as it carries sperm out of the body through the penis. The flow of urine through the urethra is controlled by the internal and external urethral sphincter muscles. The internal urethral sphincter is made of smooth muscle and opens involuntarily when the bladder reaches a certain set level of distention. The opening of the internal sphincter results in the sensation of needing to urinate.

The external urethral sphincter is made of skeletal muscle and may be opened to allow urine to pass through the urethra or may be held closed to delay urination. The kidneys maintain the homeostasis of several important internal conditions by controlling the excretion of substances out of the body.

Ions: The kidney can control the excretion of potassium, sodium, calcium, magnesium, phosphate, and chloride ions into urine. In cases where these ions reach a higher than normal concentration, the kidneys can increase their excretion out of the body to return them to a normal level. Conversely, the kidneys can conserve these ions when they are present in lower than normal levels by allowing the ions to be reabsorbed into the blood during filtration. (See more about ions.)

pH: The kidneys monitor and regulate the levels of hydrogen ions (H+) and bicarbonate ions in the blood to control blood pH. H+ ions are produced as a natural byproduct of the metabolism of dietary proteins and accumulate in the blood over time. The kidneys excrete excess H+ ions into urine for elimination from the body. The kidneys also conserve bicarbonate ions, which act as important pH buffers in the blood.

Osmolarity: The cells of the body need to grow in an isotonic environment in order to maintain their fluid and electrolyte balance. The kidneys maintain the body's osmotic balance by controlling the amount of water that is filtered out of the blood and excreted into urine. When a person consumes a large amount of water, the kidneys reduce their reabsorption of water to allow the excess water to be excreted in urine. This results in the production of dilute, watery urine. In the case of the body being dehydrated, the kidneys reabsorb as much water as possible back into the blood to produce highly concentrated urine full of excreted ions and wastes. The changes in excretion of water are controlled by antidiuretic hormone (ADH). ADH is produced in the hypothalamus and released by the posterior pituitary gland to help the body retain water.

Blood Pressure: The kidneys monitor the body's blood pressure to help maintain homeostasis. When blood pressure is elevated, the kidneys can help to reduce blood pressure by reducing the volume of blood in the body. The kidneys are able to reduce blood volume by reducing the reabsorption of water into the blood and producing watery, dilute urine. When blood pressure becomes too low, the kidneys can produce the enzyme renin to constrict blood vessels and produce concentrated urine, which allows more water to remain in the blood.

I- DIURETICS

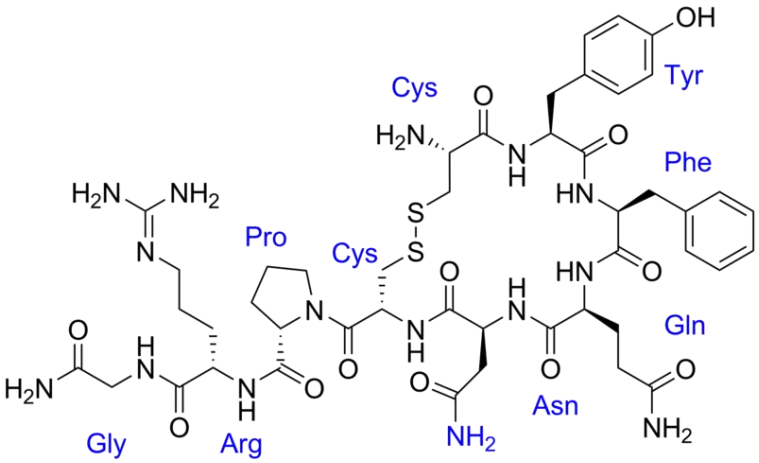
Diuretics, sometimes called water pills, help rid your body of salt (sodium) and water. Most work by making your kidneys release more sodium into your urine. The sodium then takes water with it from your blood. That decreases the amount of fluid flowing through your blood vessels, which reduces pressure on your vessel walls.

Diuretics Classification

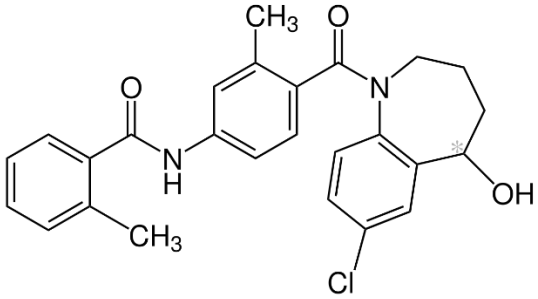
1. Vasopressin antagonists
2. Carbonic Anhydrase Inhibitors
3. Loop Diuretics
4. Osmotic Diuretics
5. K Sparing diuretics
6. Thiazides
7. Xanthines

1. Vasopressin antagonists

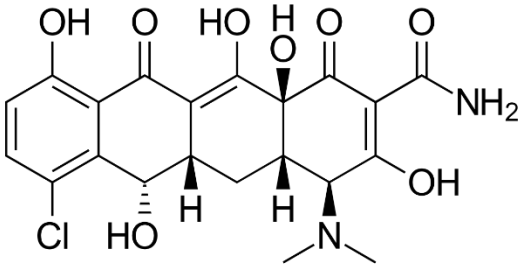
Vasopressin antagonists are drugs that bind to vasopressin receptors (V1A, V1B and V2) and block the action of vasopressin (antidiuretic hormone, ADH), which is a hormone released by the pituitary gland. Vasopressin causes vasoconstriction and increases reabsorption of water by the kidneys. V1A and V2 receptors are found peripherally and V1A and V1B receptors are found in the central nervous system. V1A receptors regulate blood pressure and V2 receptors have an effect on renal function. Vasopressin antagonists are used to treat hyponatremia particularly in congestive heart failurepatients.



Antidiuretic Hormone (ADH)



Tolvaptan



Demeclocycline

2. Carbonic Anhydrase Inhibitors

Carbonic anhydrase enzyme

The carbonic anhydrases (or carbonate dehydratases) form a family of enzymes that catalyze the rapid interconversion of carbon dioxide and water to bicarbonate and protons (or vice versa), a reversible reaction that occurs relatively slowly in the absence of a catalyst. Carbon dioxide (CO_2) is a key metabolite in all living organisms. Carbon dioxide exists in equilibrium with bicarbonate (HCO_3^-), which is poorly soluble in lipid membranes compared to carbon dioxide; carbon dioxide can freely diffuse in and out of the cell, while bicarbonate must be transported. The conversion of bicarbonate to carbon dioxide facilitates its transport into the cell, while the conversion of carbon dioxide to bicarbonate helps trap the carbon dioxide in the

cell. The interconversion of carbon dioxide and bicarbonate proceeds slowly at physiological pH, so organisms produce enzymes to speed up the process. Carbonic anhydrases are zinc-containing enzymes that catalyse the reversible reaction between carbon dioxide hydration and bicarbonate dehydration. Carbonic anhydrases have been found in all kingdoms of life. They have essential roles in facilitating the transport of carbon dioxide and protons in the intracellular space, across biological membranes and in the layers of the extracellular space; they are also involved in many other processes, from respiration and photosynthesis in eukaryotes to cyanate degradation in prokaryotes.

Mechanism of action: Carbonic anhydrase catalyses the following reaction:

$$H_2O + CO_2 \text{ ßà } H^+ + HCO_3^-$$

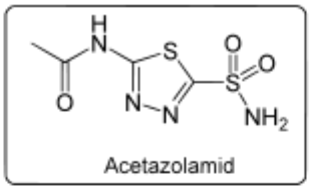
This reaction is ubiquitous in nature, involving the interchange of gaseous and ionic species crucial to a wide range of physiological and biochemical processes. The mechanism of action of the mammalian carbonic anhydrase has been studied in depth. The enzyme employs a two-step mechanism: in the first step, there is a nucleophilic attack of a zinc-bound hydroxide ion on carbon dioxide; in the second step, the active site is regenerated by the ionisation of the zinc-bound water molecule and the removal of a proton from the active site. The active site can exist in two forms: a high pH form that is active in the hydration of carbon dioxide and a low pH form that is active in the dehydration of bicarbonate.

Carbonic anhydrase inhibitors

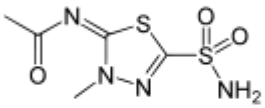
Carbonic anhydrase inhibitors reduce the activity of carbonic anhydrase, an enzyme responsible for catalyzing the reaction between carbon dioxide and water into carbonic acid and then bicarbonate. This reduces the resorption of bicarbonate from the proximal tubule in the kidneys, which causes a direct increase in bicarbonate excretion and mild increases in sodium, and potassium excretion. Generally, the electrolyte effects of carbonic anhydrase inhibitors are mild and they are typically not used for their diuretic capacity. Acetazolamide, dichlorphenamide, and methazolamide are carbonic anhydrase inhibitors.

Carbonic anhydrase inhibitors also decrease the secretion of aqueous humor (the aqueous humor is the clear fluid that fills the space between the lens and the cornea of the eyeball), which results in a decrease in intraocular pressure.

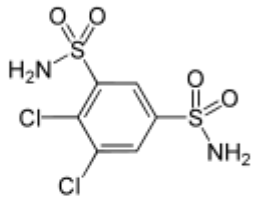
Carbonic anhydrase inhibitors are mainly used for the treatment of glaucoma or other ocular conditions where lowering of the intraocular blood pressure has been deemed beneficial. Acetazolamide is also used for the treatment and prevention of acute mountain sickness (also known as altitude sickness) and in some types of epilepsy. Dichlorphenamide may be used to treat certain inherited muscle disorders. Carbonic anhydrase inhibitors may be also used in the treatment of other conditions.



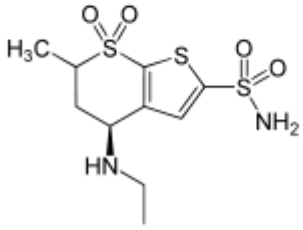
Acetazolamid



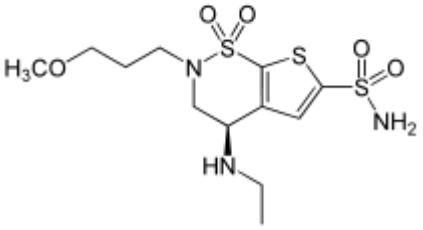
Methazolamid



Dichlorphenamid



Dorzolamid

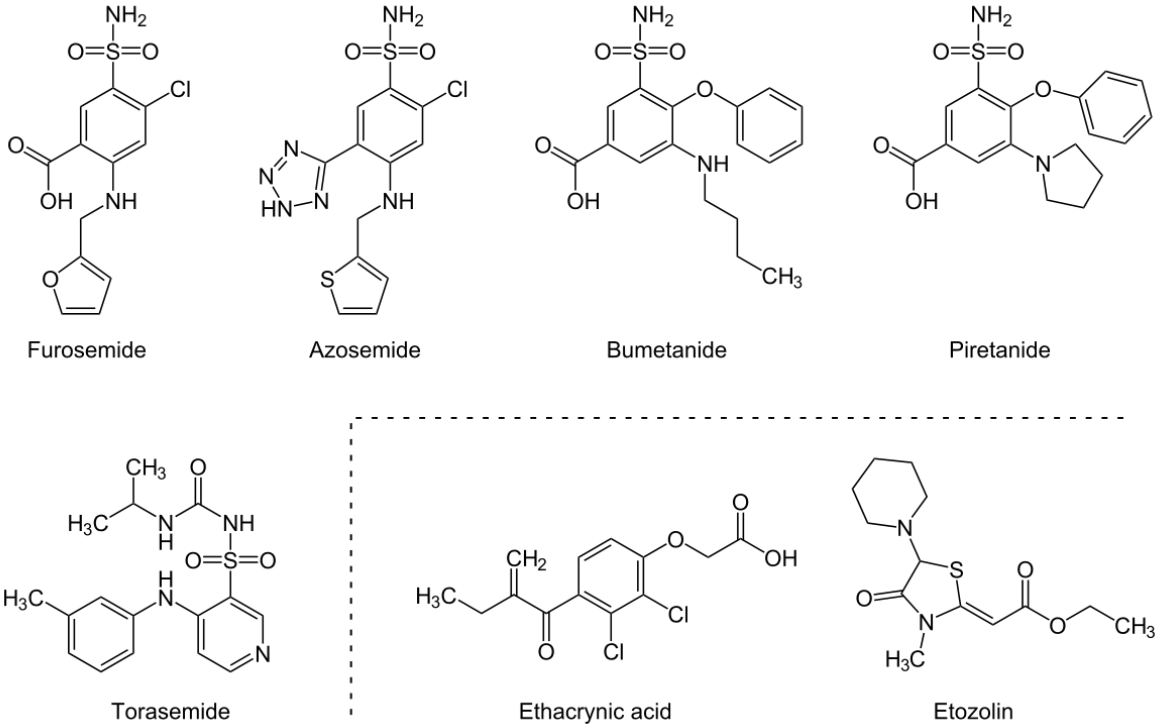


Brinzolamid

3. Loop Diuretics

Loop diuretics are diuretics that act at the ascending limb of the loop of Henle in the kidney. They are primarily used in medicine to treat hypertension and edema often due to congestive heart failure or renal insufficiency. Diuretics are medicines that increase urine flow (cause diuresis). Loop diuretics are a powerful type of diuretic that work by inhibiting the sodium-potassium-chloride (Na+/K+/2Cl) co-transporter in the thick ascending loop of Henle (hence the name loop diuretic), which is located in the kidneys. This reduces or abolishes sodium, chloride, and potassium reabsorption, leading to increased loss of sodium, chloride, and

potassium into the nephron (the functional unit of a kidney). As a result, water is also drawn into the nephron and urine volume increases. Loop diuretics also reduce the reabsorption of calcium and magnesium. Loop diuretics are used in the treatment of edema due to heart failure, liver disease and kidney disease. They may also be used to treat high blood pressure.

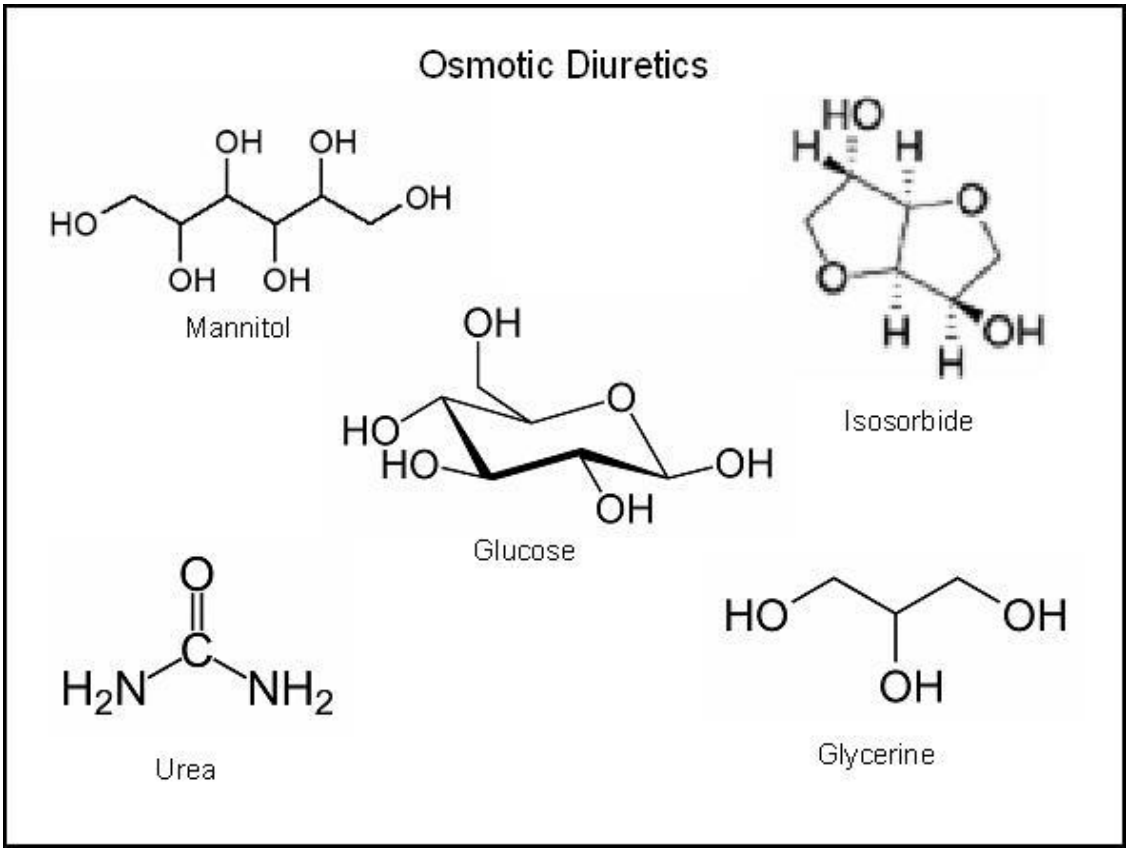


4. Osmotic Diuretics

An osmotic diuretic is a type of diuretic that inhibits reabsorption of water and sodium (Na). They are pharmacologically inert substances that are given intravenously. They increase the osmolarity of blood and renal filtrate. Osmotic diuretics are used to increase water excretion in preference to Na^+ excretion. Urine volume can be maintained even when the glomerular filtration (GFR) rate is low. The term osmotic diuretic applies to compounds which are freely filtered by the glomerulus, are not reabsorbed by the renal tubule, are generally inert from a pharmacological point of view and can thus be given in large quantity.

At the level of the proximal tubule, there is an active reabsorption of salts and a passive reabsorption of water to keep an iso-osmotic equilibrium with that of the plasma. The presence

of a high concentration of an osmotic diuretic in the lumen of the nephron increases the osmolality and decreases the reabsorption of water and electrolytes.



5. K Sparing diuretics

They act at the level of the distal part of the nephron increasing the urinary elimination of sodium and reducing that of potassium which explains their name potassium-sparing diuretics. One distinguishes two types of distal diuretics: aldosterone antagonists and those which have effects rather similar to those of antialdostérones but which act by different mechanisms.

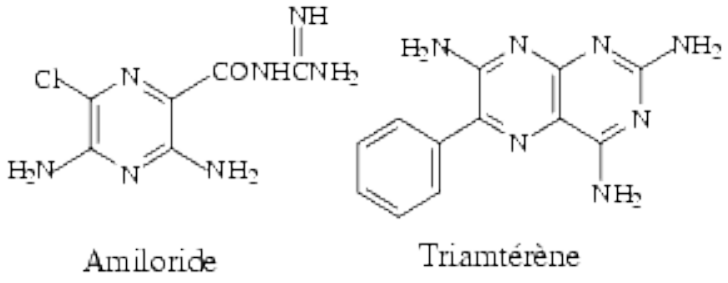
Aldosterone antagonists

Aldosterone induces the retention of sodium and the elimination of potassium (See "Mineralocorticoid: Aldosterone and Antagonists"). Aldosterone antagonists currently used are spironolactone and potassium canrenoate which acts after its conversion into canrenone. They have effects opposite to that of aldosterone, they increase the elimination of sodium and decrease that of potassium and magnesium whose plasma concentration tends to rise. They are hyperkalemic diuretics. Aldosterone antagonists are without effect in a surrenalectomized

animal or in a subject not secreting aldosterone. They could inhibit the transport of aldosterone in the cytosol of the epithelial cells of the nephron. They could also decrease aldosterone synthesis. Aldosterone antagonists have a slow and delayed effect. They have a positive inotropic action in addition. Because of their chemical steroidal structure aldosterone antagonists can give endocrine adverse effects, erectile dysfunction and gynecomastia in men, menstruation disorders and amenorrhea in women. They are indicated for the treatment of primary hyperaldosteronism and edema secondary to cirrhosis, nephrotic syndrome or congestive heart failure and essential arterial hypertension.

Amiloride and triamterene

Amiloride is not an aldosterone antagonist, because its effects are preserved in the absence of aldosterone secretion. It induces, by a direct mechanism at the distal portion of the renal tubule, an increase in urinary excretion of sodium and decrease in magnesium and potassium excretion by inhibiting the exchange Na+/K+. Its mechanism of action is still poorly understood, it initially inhibits sodium reabsorption and secondarily potassium excretion.



Amiloride Triamtérène

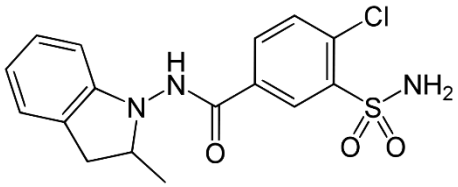
Amiloride is an hyperkalemic diuretic often used in combination with an hypokalemic thiazide diuretic to reduce the risk of hypokalemia. It decreases the urinary calcium loss. Amiloride was proposed in aerosol for the treatment of cystic fibrosis where an excessive sodium absorption and a defect of chloride secretion induce a dryness of the bronchial membranes. The effects of triamterene are quite similar to those of amiloride. Triamterene is released on the market in combination with a thiazide diuretic. It can give urinary calculuses.

6. Thiazides

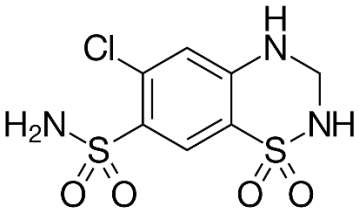
Thiazide diuretics inhibit the cotransport of symport type Cl/Na^+ in the initial part of the distal tubule, after having been secreted in the lumen of the proximal tubule.

Thiazides reduce the reabsorption of Cl^- and Na^+, primarily by inhibiting their cotransport, especially at the level of the initial part of the distal convoluted tubule where less than 10% of Na^+ and Cl filtered by the glomerulus remains. The mechanism and their location of action explain their relatively moderate diuretic effect because they act on a low proportion of the sodium filtered by the glomerulus. Thiazide diuretics increase also urinary potassium elimination but to a lesser extent than sodium. This increase, which remains moderate, is badly explained; it could be the indirect effect of the increase in its secretion by the distal tract. Thiazide diuretics also increase the urinary magnesium elimination. They increase the elimination of bromide and of iodide parallel to that of chloride like that of bicarbonates and the pH of the urine rises. They decrease the urinary calcium elimination, which improves the calcium balance. Used over a long time, they decrease in the elderly the risks of fracture of the hip. They increase the aqueous diuresis moderately.

In plasma, they decrease the potassium concentration, they are hypokalemic diuretics. They slightly increase plasma uric acid concentration by decreasing its tubular secretion. The paradoxical antidiuretic action of thiazide diuretics observed in patients with diabetes insipidus is not well explained, sodium depletion could be responsible.



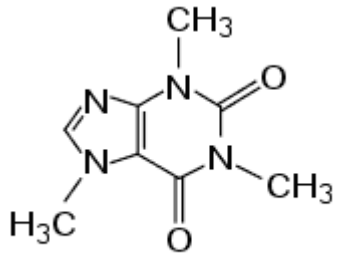
Indapamide



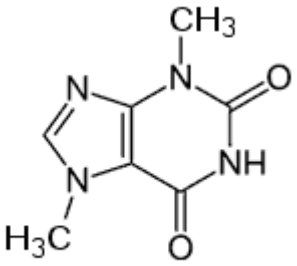
Hydrochlorothiazide

7. Xanthines

Xanthine (3,7-dihydropurine-2,6-dione), is a purine base found in most human body tissues and fluids and in other organisms. A number of stimulants are derived from xanthine, including caffeine and theobromine. Xanthine is a product on the pathway of purine degradation.



caffeine



theobromine

II. FLUID AND ELECTROLYTE IMBALANCE DRUGS

Electrolytes are minerals in your body that have an electric charge. They are in your blood, urine, tissues, and other body fluids. Electrolytes are important because they help

- Balance the amount of water in your body
- Balance your body's acid/base (pH) level
- Move nutrients into your cells
- Move wastes out of your cells
- Make sure that your nerves, muscles, the heart, and the brain work the way they should

Sodium, calcium, potassium, chlorine, phosphate, and magnesium are all electrolytes. You get them from the foods you eat and the fluids you drink.

The levels of electrolytes in your body can become too low or too high. This can happen when the amount of water in your body changes. The amount of water that you take in should equal the amount you lose. If something upsets this balance, you may have too little water (dehydration) or too much water (overhydration). Some medicines, vomiting, diarrhea, sweating, and liver or kidney problems can all upset your water balance.

Treatment helps you to manage the imbalance. It also involves identifying and treating what caused the imbalance. Treating electrolyte imbalances caused by kidney failure can be difficult, because many medicines lower some electrolyte levels while raising other levels. Your doctor may need to regularly monitor your electrolyte levels.

Potassium: Severe chronic kidney disease and kidney failure can increase potassiumlevels above the normal range (hyperkalemia). Medicines used to lower potassium levels may include:

- Potassium binders, such as sodium polystyrene sulfonate (Kayexalate).

- Diuretics , which increase the amount of potassium released by the kidneys through the urine. This may be an option if you have some remaining kidney function.

Hemodialysis is the best way to lower potassium levels if kidney failure has developed rapidly and potassium levels are very high.

Calcium and phosphorus: Kidney failure causes an increased breakdown of bone and abnormal metabolism of calcium, phosphorus, vitamin D, and parathyroid hormone (PTH). This often leads to a bone disease called renal osteodystrophy. Medicines used to restore proper metabolism of these chemicals may include:

- Calcium-containing phosphate binders, such as calcium acetate and calcium carbonate. They are used to raise levels of calcium and lower levels of phosphorus in the bloodstream. Phosphate binders that contain aluminum should be avoided, to prevent aluminum poisoning.
- Non-calcium phosphate binders, which are calcium- and aluminum-free. Examples are sevelamer and lanthanum. They are also used to control serum phosphate and reduce PTH levels.
- Vitamin D3 , which may increase calcium levels and help store excess phosphate in bone. While taking vitamin D3, you will be watched closely for hypercalcemia.

III. ACID-BASE IMBALANCE DRUGS

Your blood needs the right balance of acidic and basic (alkaline) compounds to function properly. This is called the acid-base balance. Your kidneys and lungs work to maintain the acid-base balance. Even slight variations from the normal range can have significant effects on your vital organs. Acid and alkaline levels are measured on a pH scale. An increase in acidity causes pH levels to fall. An increase in alkaline causes pH levels to rise. When the levels of acid in your blood are too high, it's called acidosis. When your blood is too alkaline, it is called alkalosis. Respiratory acidosis and alkalosis are due to a problem with the lungs. Metabolic acidosis and alkalosis are due to a problem with the kidneys. Each of these conditions is caused by an underlying disease or disorder. Treatment depends on the cause.

Metabolic acidosis: Metabolic acidosis occurs either when your body produces too much acid, or when your kidneys are unable to remove it properly. Symptoms of metabolic acidosis include rapid breathing, fatigue, and confusion. Causes of metabolic acidosis: There are three main types of metabolic acidosis. Diabetic acidosis, or diabetic ketoacidosis, is a buildup of ketone bodies. This is usually due to uncontrolled type 1 diabetes. Hyperchloremic acidosis is when your body loses too much sodium bicarbonate, often after severe diarrhea. Treatment of metabolic acidosis; The underlying condition behind the acidosis must be treated. In some cases, sodium bicarbonate is prescribed to return the blood to a normal pH. Complications of metabolic acidosis: Severe cases can lead to shock and can be life threatening.

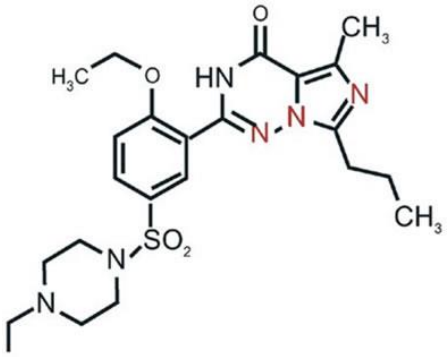
Alkalosis: Alkalosis is when alkaline levels are too high due to decreased carbon dioxide or increased bicarbonate. There are five kinds of alkalosis. Symptoms of alkalosis include:

- muscle twitching, hand tremor, muscle spasms
- numbness and tingling
- nausea
- vomiting
- lightheadedness
- confusion

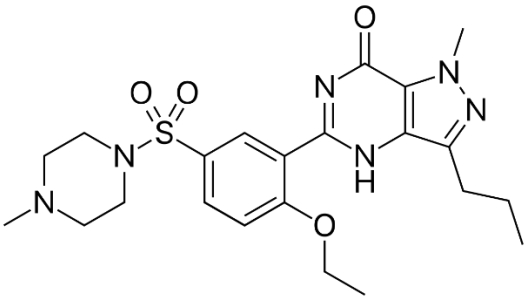
When you have alkalosis your carbon dioxide levels are low. This causes your body to release more bicarbonate to return your blood pH level back to normal. This is called compensated alkalosis. Your blood pH levels will test normal, however your kidneys are releasing more bicarbonate, compensating for the lower levels of carbon dioxide. When your blood has too much bicarbonate, it is called metabolic alkalosis. This can happen from prolonged vomiting. Prolonged vomiting can also make you lose too much chloride. This is called hypochloremic alkalosis. Some diuretic medicines can cause you to lose too much potassium. This is called hypokalemic alkalosis. Treatment for alkalosis; Some medications (such as chloride and potassium) can help correct chemical losses. Further treatment will depend on the cause. Your physician will need to monitor your vital signs and create a proper plan to correct your pH imbalance.

IV. ANTIIMPOTENCE AGENTS

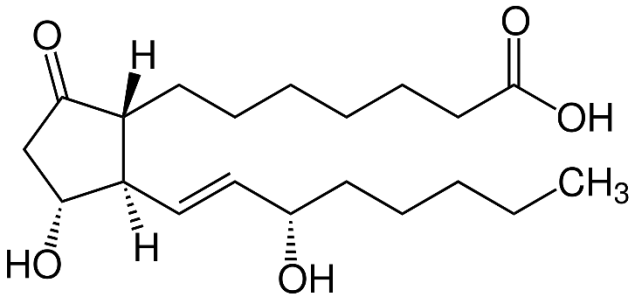
Impotence agents treat erectile dysfunction and enable men to have sexual intercourse. Generally, they cause vasodilatation and increase blood flow to the penis and cause an erection.



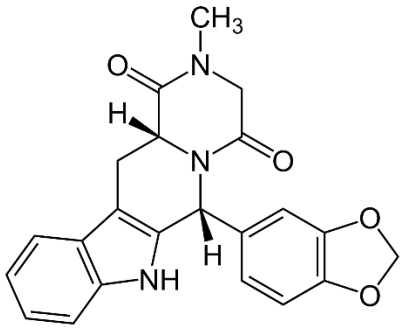
Vardenafil



Sildenafil



Alprostadil



Tadalafil

- impotence agents
- Diuretics
- miscellaneous genitourinary tract agents
- tocolytic agents
- urinary antispasmodics
- urinary pH modifiers
- uterotonic agents