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Therapeutic role of diuretics across various clinical disorders

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Abstract
Diuretic drugs are class of pharmaceutical agents that promote diuresis, or increased urine production, by acting on different segments of the nephron to inhibit sodium and water reabsorption. They play a pivotal role in the management of several clinical conditions, particularly those associated with fluid overload and hypertension. Diuretics are broadly classified into loop diuretics, thiazide diuretics, potassium- sparing diuretics, osmotic diuretics and carbonic anhydrase inhibitors—each differing their site of action and therapeutic application. This article explores the underlying mechanisms of action of various diuretic classes and reviews their clinical use in treating disorders such as congestive heart failure, chronic kidney disease, Glaucoma, liver cirrhosis and hypertension. Emphasis is placed on the pharmacodynamics, potential adverse effects and appropriate selection of diuretics tailored to specific pathologies. Underlying the pharmacological basis and therapeutic indications of diuretics is essential for optimizing patient outcomes and minimizing complications associated with their use.

Keywords: Diuretics, diuresis, sodium reabsorption, nephron, loop diuretics, hypertension, liver cirrhosis, adverse effects, fluid overload, clinical use, patient outcomes

Introduction

Diuretics, often referred to as water pills, are medications that help your body, eliminate excess fluid and salt by increasing the amount of urine your kidneys produce [1]. Most people are instructed to take their diuretic dose once or twice daily, ideally at the same time each day for best results [2].

As blood flows through the kidney, it enters the glomerular capillaries located within the cortex, the kidney's outer zone. The hydrostatic pressure within the glomerular capillaries drives the filtration of water and electrolytes into Bowman's capsule, from where the filtrate enters the proximal convoluted tubule (PCT). Roughly 65-70% of the filtered sodium is reabsorbed here, a process known as sodium reabsorption. This occurs iso-osmotically, meaning that each sodium ion reabsorbed is accompanied by a corresponding water molecule. As the tubule descends into the medulla (the kidney's inner zone) it narrows to form the loop of Henle. This water loss concentrates the tubular fluid within the loop, producing more concentrated urine [3, 4].

Over the last four decades, numerous classes of diuretics that are currently accessible for clinical usage have been the preferred treatment for a wide range of cardiovascular and noncardiovascular illnesses. Traditional diuretics are frequently recommended to treat hypertension, oedema, and heart failure, as well as a variety of renal issues. They are diseases with significant mortality rates, and the number of patients suffering from heart and renal disease is growing year after year.

- **Diuresis:** Diuresis is defined as excessive urine output caused by increased renal filtration of body fluids. While healthy adults normally urinate 4-6 times per day, with an output of about 0.7-3 litres, people with diuresis have increased frequency and volume without increasing fluid consumption.
- **Causes of diuresis:** Diuresis can be caused by certain medical problems or by taking drugs that stimulate urine production. Lifestyle variables can also influence its growth. Excessive urination produced by diuresis can induce dehydration, and without appropriate hydration, the body may struggle to maintain its temperature. In severe situations, this might result in renal damage, convulsions, or even shock [5].
- **Renal Anatomy and Physiology:** The glomerulus and formation of ultra filtrate

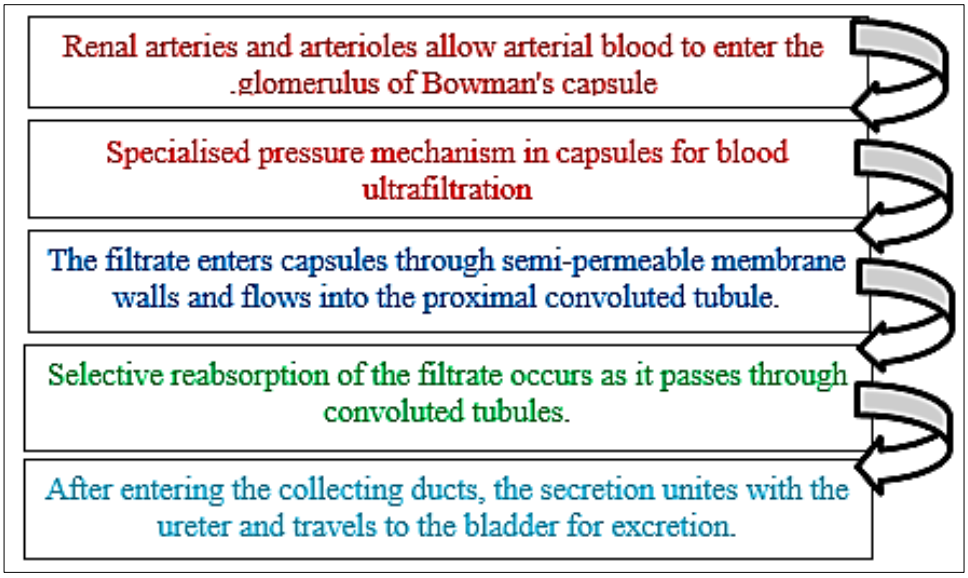


Fig 1: Schematic flow chart of urine production

Diuretics help the kidneys remove excess salt and water from the body by excreting them into the urine. By eliminating this extra fluid, diuretics reduce the volume of blood that the heart needs to pump. This action is beneficial for people with kidney problems, swelling (oedema), heart failure, or high blood pressure.

- **Renal Anatomy and Physiology:** The glomerulus and formation of ultra filtrate

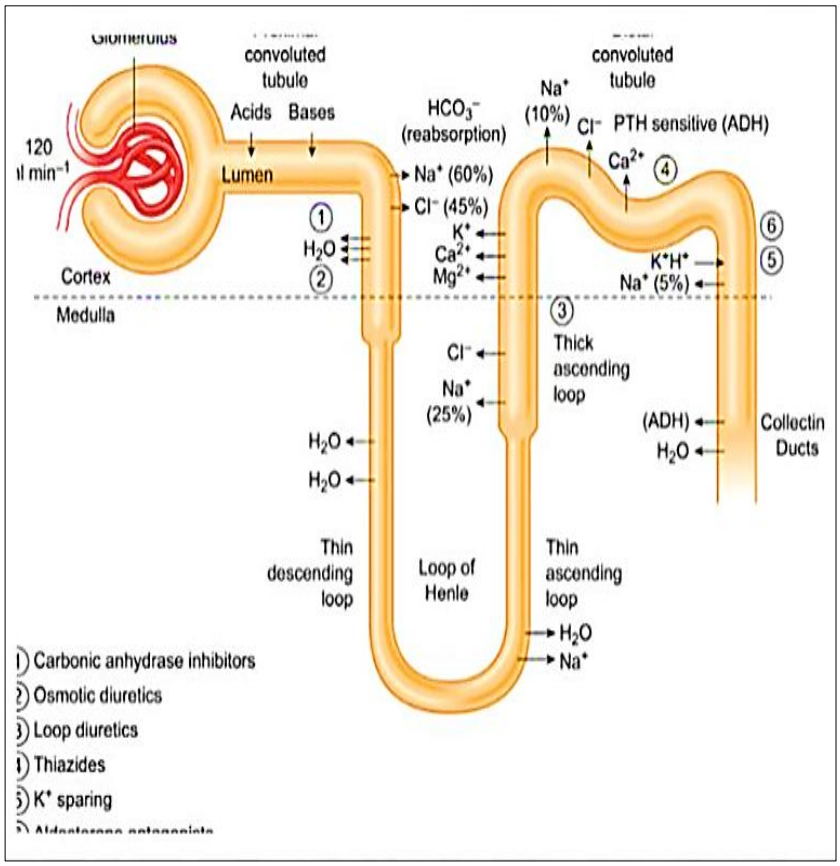


Fig 2: Sites of action of diuretics along the nephron. ADH, Antidiuretic hormone; PTH, parathyroid hormone.

An afferent arteriole supplies blood to each of the 800,000-1,000,000 nephrons that make up a typical kidney (Fig.1). the glomerulus, a collection of Capillaries inside Bowman's capsule, is formed by the afferent arteriole. The glomerular capillaries fenestrated endothelium, the glomerular basement membrane, and the visceral epithelial cells(podocytes) all contribute to the formation of the ultrafiltrate.[6]The negatively charged glycocalyx prevents negatively charged proteins like albumin from filtering through, while these layers function as a semipermeable membrane that permits the flow of fluids, solutes, and proteins smaller than 70kDa.

2. Classification of diuretics & its mechanism

2.1. Classification of diuretics

Table 1: Classification of diuretics and their action

Class of diuretics	Site of action	Mechanism	Examples
Carbonic-anhydrase Inhibitors	Proximal tubule	Inhibition of carbonic anhydrase	Acetazolamide
Loop diuretics	Loop of Henle (TAL) Proximal tubule	Inhibition of Na^+-K^+-2Cl symporter	Furosemide, Torsemide, Bumetanide
Thiazide diuretics	Distal convoluted tubule	Inhibition of Na^+-Cl symporter	Hydrochlorothiazide, Bendroflumethiazide, Chlorthalidone, Indapamide Xipamide
Osmotic diuretics	Proximal tubule & Loop of Henle	Increase osmotic pressure inhibit water reabsorption	Mannitol
Potassium-sparing diuretics	Collecting duct	**ENaC inhibitors**: block Epithelial $Na^{\pm}$ channel **Aldosterone-Antagonists:** block aldosterone receptor	•**ENaC inhibitors:** Amiloride, Triamterene •**Aldosterone Antagonists:** spironolactone, Eplerenone

2.2. Mechanism of diuretics

2.2.1. Carbonic anhydrase inhibitors: (Acetazolamide) Carbonic acid (H_2CO_3) is typically formed in the renal tubules by the combination of locally released hydrogen ions with filtered bicarbonate (HCO_3^-). In turn, carbonic anhydrase typically reacts with carbonic acid to produce

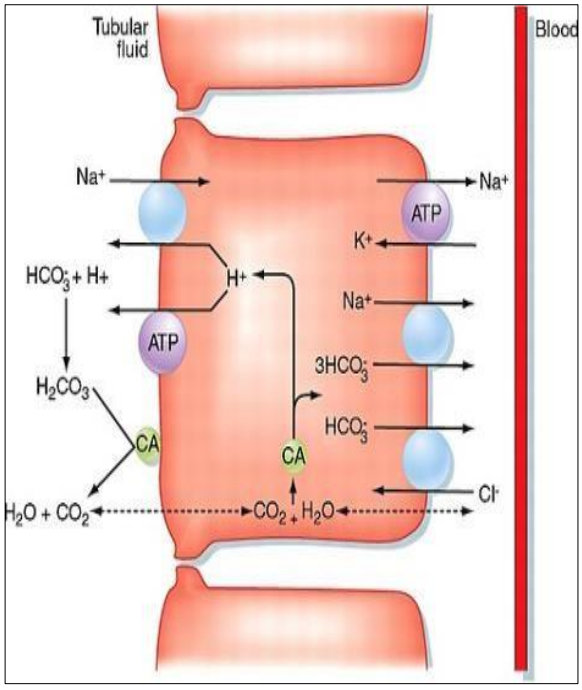
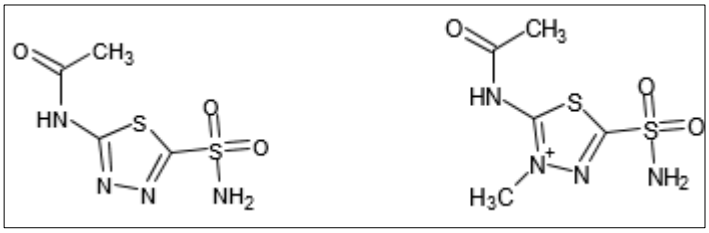


Fig 3: Mechanism of action of acetazolamide

Co_2. However, carbonic acids levels rise and carbonic anhydrase is blocked when acetazolamide is present. Urinary bicarbonate waste results from the suppression of carbonic anhydrase, which also slows down the reverse reaction and reduces the body's capacity to reabsorb serum bicarbonate. This results in a mild diuresis because the kidney's proximal convoluted tubules are less able to exchange Na^+ for H^+ when acetazolamide is present.



Acetazolamide Methazolamide

Acetazolamide Methazolamide

2.2.2 Thiazide diuretics: These thiazide diuretics mainly blocks the sodium transport in the distal tubule [7, 8]. It connecting segment at the end, and may be the early cortical collecting tubule [9, 10]. Through competition for the chloride site on the transporters, the thiazides prevent NaCl reabsorption in these segments [11]. Certain medications, such as chlorothiazide, also highly reduce salt transport in the proximal tubule because they partially inhibit carbonic Anhydrase [12]

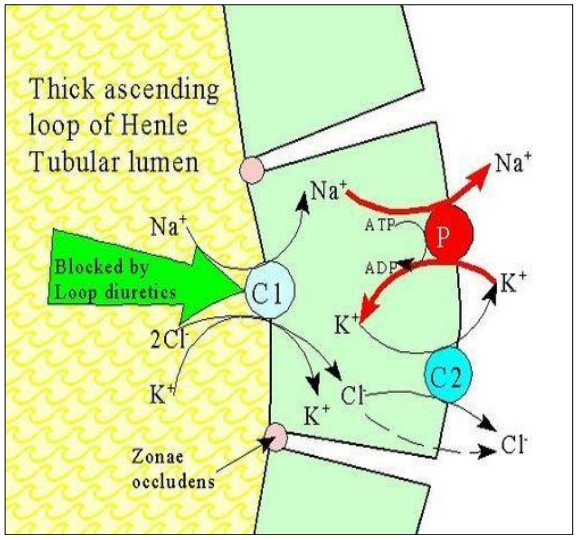


Fig 4: Mechanism of action of Thiazide diuretics

2.2.3 Osmotic diuretics:

Osmotic diuretics are freely filterable but not reabsorbed and prevent H_2O reabsorption in the proximal tubule. Osmotic diuretics also extract H_2O from systemic body compartments. This expands extracellular fluid volume increases renal blood flow. This increase in blood flow removes NaCl and urea from to renal medulla [13].

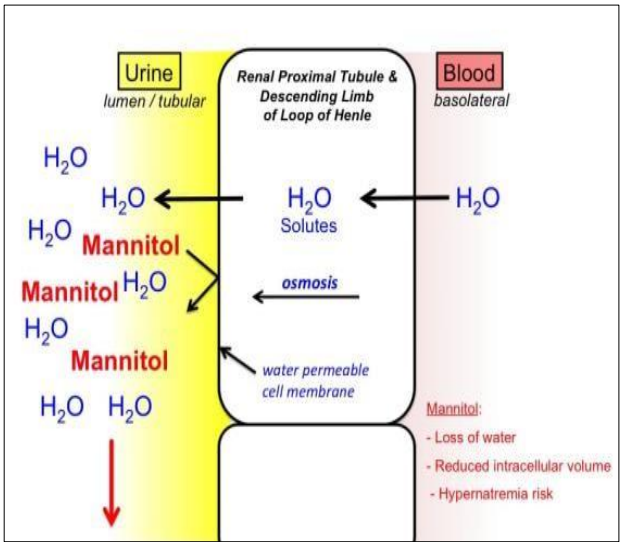


Fig 5: Mechanism of action of osmotic diuretic

Mannitol

3. Therapeutic uses of diuretics in the management of various diseases

Diuretics are commonly prescribed for diseases such as hypertension, liver cirrhosis with ascites, heart failure, oedema and certain kidney disorders. Their utility extends to improving symptoms related to fluid overload and helping the body maintain a healthier fluid balance.

3.1 hypertension

For many years, diuretics have been used to manage high blood pressure. Several clinical trials have proven its effectiveness. Diuretics are the earliest and first antihypertensive medications to show efficacy with tolerable side effects. A significant shift in the management of arterial hypertension was brought about by their introduction into therapeutics in the 1950s. Their overall mode of action involves altering ion transport at several nephron sites and promoting the excretion of water and electrolytes, mainly sodium and chloride, by the kidneys. The mechanism and place of action of diuretics are used to classify them. Such as potassium-sparing diuretics, osmotic, thiazide, loop, or high ceiling, and carbonic anhydrase inhibitors. Thiazides are the most widely used antihypertensives, and they are occasionally used with potassium -sparing diuretics. Only certain situations call for the use of loop diuretics.

Role of diuretics in management of Hypertension

In the first randomized clinical trials, done in the 1960s, diuretic-based hypertension treatment was found to be useful in lowering stroke and heart disease risk. This "track record" has remained successful in most recent trials, as indicated in ALLHAT [14]. Despite this, diuretics can be divided into three subclasses, each of which is critical to treating the majority of hypertension patients. Drug development has occurred within the diuretic class, despite the fact that the bulk of them have been utilized in clinical settings for any years. We'll focus on three types of diuretics used to treat high blood pressure: (1) Thiazide-type, (2) loop-active, and (3) potassium-sparing drugs that operate as sodium channel inhibitors or mineralocorticoid antagonists in the late distal renal tubule or collecting duct.

Loop-Active Agents: In the distal renal tubule at the ascending limb of the loop of the Henle, furosemide and its analogues (bumetanide and torsemide) block the reabsorption of potassium, sodium, and calcium at locations different from the thiazide-sensitive loci. These loop-active medications must be used twice daily to treat hypertension due to their brief duration of action.

3.2. Liver Cirrhosis

Spironolactone is the cornerstone of diuretic treatment for cirrhosis patients with oedema since secondary hyperaldosteronism is a major contributor to their water and sodium retention [15]. It is preferable that spironolactone only produces a mild diuresis because higher diuresis could jeopardies the intravascular volume. (16) Spironolactone is typically started at a dose of 50mg daily. Because the half-lives of the medication and its active metabolites are long enough, once daily administration is sufficient [15, 17]. Doses over 200 mg daily are frequently poorly tolerated, however the dosage can be raised to 400 mg daily. Depending on the degree of renal function, a thiazide diuretic may be added if maximal doses of spironolactone are insufficient to produce an acceptable diuresis. As spironolactone is being used, a loop diuretic may be administered in place of the thiazide if diuresis is still insufficient.

In conclusion, spironolactone serves as the cornerstone of diuretic therapy for cirrhosis patients, with thiazides, loop diuretics, or both added as needed. A thiazide or loop diuretic should not be used in large amounts all at once; rather moderate dosages should be taken multiple times a day and diuretic sodium restriction should be promoted.

3.3. Nephrotic syndrome

The symptoms of nephrotic syndrome include proteinuria, oedema, hypoalbuminemia, and hyperlipidaemia. Nephrotic syndrome effects roughly three out of every 100,000 adults annually [18]. Treatment for nephrotic syndrome involves reducing proteinuria and causing diuresis to lessen fluid excess in addition to managing the underlying condition. Making the sodium balance negative is essential to a successful course of treatment. Patients are instructed to take diuretics and limit their daily fluid intake to 1.5 liters, as well as their sodium intake less than 100 mmol (3g). Less serum albumin levels cause diuretics to diffuse more widely through the extracellular space. For the active site to have sufficient amounts of loop diuretic, albumin and diuretic may be required. The combination of thiazides and loop diuretics has been shown to improve overall efficacy [19]. Comparison between the thiazide-furosemide and Metolazone-furosemide diuretic combinations revealed that both produced comparable outcomes [20].

Administering the appropriate dosage to reach the active site is the difficult part. An IV bolus of furosemide, 160-200mg, or the equivalent of bumetanide plus Torsemide, is the highest dosage, sometimes referred to as ceiling dose. Patients with volume expansion received oral spironolactone at 2.5 mg/kg per dosage, divided twice daily, up to 100mg, and intravenous furosemide at mg/kg per dose, up to 40mg, twice daily. According to the study's findings, diuretics alone were a safe and efficient treatment for children [21].

3.4. Glaucoma

Glaucoma is athe most common cause of irreversible blindness, affecting an estimated 67 million people. It usually affects people over 40, although it can also affect younger people, including kids. A rise in intraocular pressure (IOP) that damages the optic disc and causes disruptions in the visual field is referred to as glaucoma. The long-term treatment of glaucoma involves a variety of drug classes, such as prostaglandin analogues, carbonic anhydrase inhibitors, beta-adrenergic blockers, miotics etc. The long-term treatment of glaucoma involves a variety of drug classes, such as prostaglandin analogues, carbonic anhydrase inhibitors, beta-adrenergic blockers, miotics etc.

Carbonic anhydrase inhibitors: carbonic anhydrase inhibitors can be taken be available as eye drops such as brinzolamide or dorzolamide, or as oral formulations. Acetazolamide is a light or weak diuretic that can be taken orally to treat glaucoma. It lessens the possibility of fluid accumulation in the eye. Since acetazolamide's effectiveness can diminish with time, it is often only taken for brief periods of time.

3.5. Pregnancy

Cardiovascular disease is a leading cause of maternal mortality and morbidity worldwide. As surgical and therapeutic care improves, more women with congenital heart disease reach reproductive age and become pregnant. [22, 23]. As a result, the usage of medications to treat cardiovascular illnesses is projected to increase over time. Pregnancy causes pharmacokinetic alterations due to increased total body water, liver metabolism, and glomerular filtration rate.

Diuretics reduce plasma volume and venous pressure by altering the balance of sodium and water. Using diuretics during pregnancy may also have an effect on placental perfusion, which could harm foetal growth, according to this mechanism. Studies on the use of diuretics during pregnancy, however, have shown conflicting findings about the outcomes for the fetus and newborn [24].

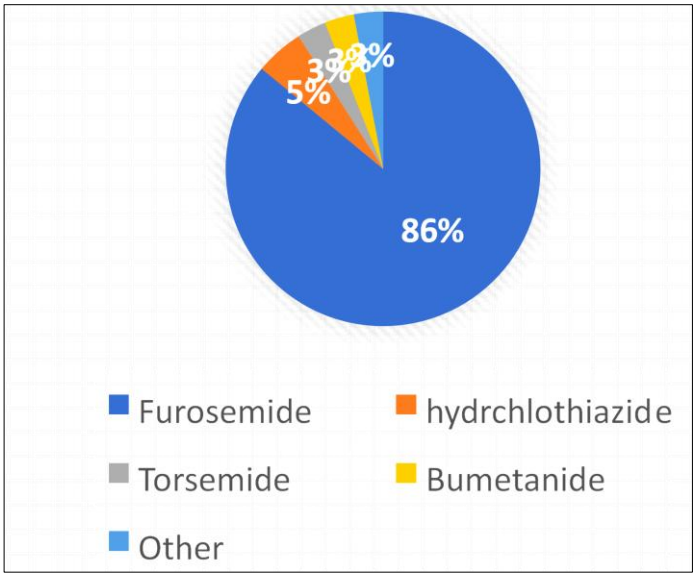


Fig 6: Types and frequency of diuretics prescribed during pregnancy

3.6. Diuretic in diagnosis

Diuretics are commonly used as therapeutic drugs; however, furosemide has been shown to play a specific function in the diagnosis of distal renal tubular acidosis (RTA), also known as type I RTA. The furosemide-fludrocortisone test is a speedier and more appealing alternative to the ammonium chloride urine acidification test. Fludrocortisone stimulates both sodium reabsorption in the cell and α-intercalated hydrogen ion secretion via activating the H^+-ATPase enzyme. They argued that the combination would give an adequate and consistent stimulus to elucidate an acidification deficit in type I RTA without using ammonium chloride, which causes a systemic acid load to be expelled [25].

Diuretic abuse

Abuse of diuretics unfortunately, in cases where there is no actual therapeutic indication, people may decide to take diuretics improperly on their own. Hypokalaemia, which is typically linked to eating disorders like bulimia or anorexia nervosa, can be lethal.

4. Risks/benefits & Adverse effects

4.1. What are the advantages of diuretic?

Many people get positive outcomes with diuretic tablets, particularly when taking them to manage high blood pressure. Furthermore, diuretics seldom cause negative side effects in persons. While some natural remedies, such as herbal supplements, might be beneficial, water tablets may yield more consistent outcomes.

4.2. Side effects of diuretics?

Possible side effects of diuretics include:

- Stomach upset, gas,
- diarrhoea
- Loss of appetite
- Fatigue
- Difficulty getting an erection

4.3. Adverse effects of diuretics

- Hypomagnesemia
- Hypokalaemia and hyperkalaemia
- Metabolic abnormalities

a) Hyperglycemia
b) Hyperlipidemia

5. Future developments

A new family of diuretics has recently been discovered, posing an interesting challenge to medical science. They are known as AQP modulators and are expected to be economically exploited, as a patent application for the first in their class, AqB013, was just submitted. Dr. Peter Agre was awarded the Nobel Prize for Chemistry in 2003, 15 years after his discovery in 1988. There are eleven recognised AQP channels (AQP0-AQP10), however not all of them are present in humans. Following studies on oocytes expressing AQP1 and AQP4, one of the 45 synthesised bumetanide derivatives was discovered to inhibit AQP1 and AQP4 water permeability. There are currently few options for treating severe cerebral oedema. Therapeutic intervention is facilitated by the position of AQP4 in the perivascular glial end-feet of the brain.
However, this work is still in its infancy.

6. Self-Care and Management Guidelines While taking Diuretics

6.1. What self-care measures may I take while using a diuretic?

You can care for yourself in the following ways when taking a diuretic:

- Limit the amount of salt in diet.
- Make you don’t get dehydrated
- Get blood or urine tests your provider orders to check kidney function.

6.2. What are the responsibilities when taking a diuretic?

- Every day, take your diuretic at the same time.
- To avoid waking up in the middle of the night to urinate, avoid taking your diuretic right before bed. Prior to 6 p.m., try to take your diuretic.
- Take your first dose of your diuretic in the morning and your second dose six to eight hours later if you take it twice a day.

6.3. What if I take too much diuretic?

Overdosing on a diuretic can have serious consequences. You might encounter the following adverse effects:

- A fast or irregular heartbeat
- Nausea, vomiting
- Weakness

6.4. What to do if I miss a dose of my diuretic?

- If you forget a dose, take it as soon as you remember. If it is almost time for your next dose, skip the missing one. Return to your normal time.
- Do not take 2 doses at the same time or extra doses.

6.5. When to make doctor's consultation:

Contact your providers when have diuretic side effects that bother you, like

- Heart palpitations
- Dizziness
- Dehydration

7. Conclusion

Diuretics play a critical role in managing a range of clinical conditions characterized by fluid overload, such as hypertension, congestive heart failure, liver cirrhosis, nephrotic syndrome, and oedema. By acting on various segments of the nephron, different classes of diuretics inhibit sodium and water reabsorption to increase urine output and reduce blood volume. While generally effective and well-tolerated, diuretics require careful monitoring to prevent potential adverse effects like electrolyte imbalances, dehydration, and metabolic disturbances. Emerging therapeutic agents targeting aquaporin channels hold promise for future treatments. Patient education and adherence, along with judicious use under medical supervision, optimize therapeutic outcomes and minimize risks. Diuretics are essential medications for managing fluid overload and hypertension by promoting urine production through various mechanisms in different parts of the nephron. Their use is crucial in treating conditions like heart failure, liver cirrhosis, nephrotic syndrome, and glaucoma. With proper medical supervision and patient adherence, diuretics continue to be a cornerstone in optimizing fluid balance and improving patient outcomes across multiple diseases.

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