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A REVIEW ON DIURETIC ACTIVITY

Dev Prakash Dahiya[1], Abhishek[2]*, Anchal Sankhyan[3], Aditya Thakur[5] and Richa Kumari[6]

[1]Research Scholar, School of Pharmacy, Abhilashi.

[2]Dean, School of Pharmacy, Abhilashi University, Mandi, Himachal Pradesh.

[3]Assistant Professor, School of Pharmacy, Abhilashi University, Mandi Himachal Pradesh.

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***Corresponding Author**
Abhishek
Dean, School of Pharmacy,
Abhilashi University,
Mandi, Himachal Pradesh.

ABSTRACT

Diuretics are pharmacological agents that increase urine formation by promoting the excretion of water and electrolytes, primarily sodium and chloride, while preserving essential nutrients. They play a crucial role in managing conditions like edema, hypertension, congestive heart failure, glaucoma, hypercalcemia, diabetes insipidus, and liver cirrhosis with ascites. Diuretics are classified based on their site of action within the nephron: carbonic anhydrase inhibitors, loop diuretics, thiazide diuretics, potassium-sparing diuretics, and osmotic diuretics. Each class has a unique mechanism of action and therapeutic application. While effective, diuretics can cause side effects, such as electrolyte imbalances, metabolic disturbances, and dehydration, necessitating careful monitoring. Combination therapies often enhance diuretic efficacy while minimizing adverse effects.

INTRODUCTION

Diuretics are substances that increase the rate of urine formation by promoting the excretion of water and electrolytes, particularly sodium (Na^+) and chloride (Cl^-), from the body. They achieve this by enhancing urine flow, which helps remove excess fluids without affecting the reabsorption of essential nutrients such as proteins, vitamins, glucose, and amino acid.

Diuretics are mainly used in:

1. **Edema relief:** They help reduce fluid retention associated with conditions like heart, kidney, or liver disease.

2. **Hypertension management:** Diuretics are often used as adjuvants in the treatment of high blood pressure, where fluid reduction lowers blood volume and, consequently, blood pressure.

3. **Management of various disorders**

- Congestive Heart Failure (CHF): To alleviate fluid overload.
- Chronic and acute renal failure: To prevent fluid accumulation.
- Glaucoma: To lower intraocular pressure.
- Hypercalcemia: Certain diuretics promote calcium excretion.
- Diabetes insipidus: Thiazide diuretics help reduce excessive urination.
- Liver cirrhosis with ascites: To manage fluid buildup in the abdominal cavity.

Function of the kidneys

The kidneys play a vital role in maintaining the body's homeostasis by balancing electrolytes and water while eliminating metabolic waste products. These functions are accomplished through urine formation, which occurs in the functional units of the kidney known as nephrons.

Carbonic anhydrase inhibitors: Act primarily at the proximal convoluted tubule. Reduce bicarbonate reabsorption, increasing urinary output.

Loop diuretics: Act at the loop of Henle, specifically the thick ascending limb. They are potent diuretics, promoting significant sodium, chloride, and water excretion.

Thiazide and Thiazide-like Diuretics: Act at the distal convoluted tubule.Commonly used for hypertension and mild edema.

Potassium-Sparing diuretics: Act at the collecting tubule.Unlike other diuretics, they prevent potassium loss while promoting sodium excretion.

Osmotic diuretics: Act at the proximal tubule, loop of Henle, and collecting tubule.These diuretics increase osmotic pressure in the renal tubules, leading to water excretion.

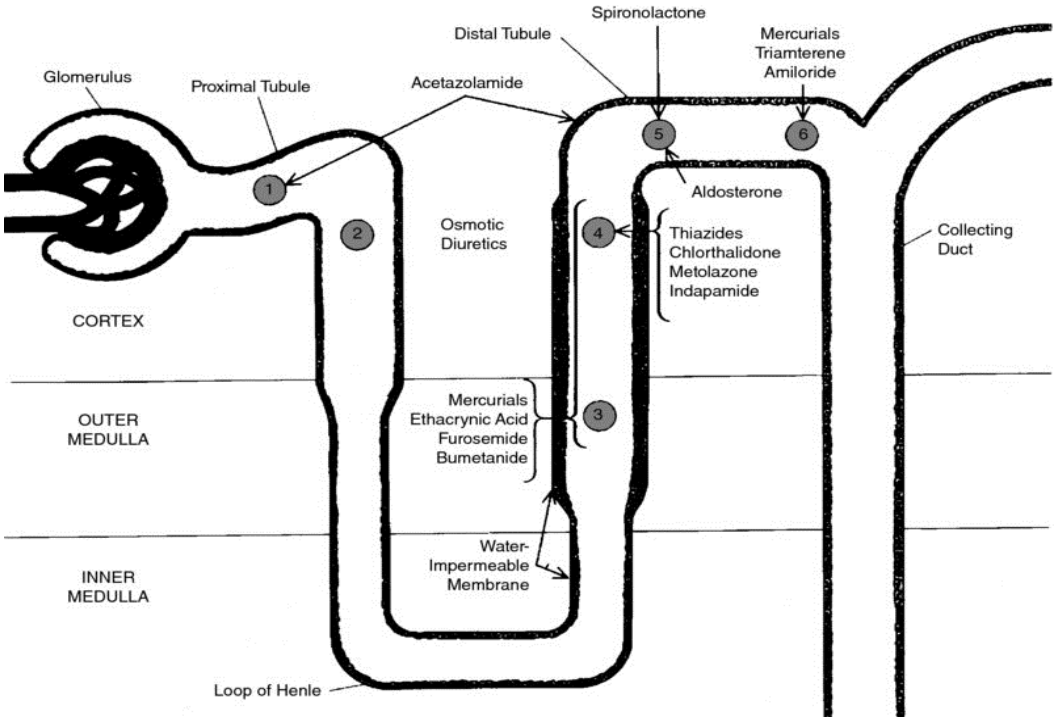

Fig. Locations the nephron where diuretic agents exert their effects.

Classification and Mechanism of diuretic drugs

Diuretic drugs increase urine production by the kidneys, promoting diuresis. They achieve this by affecting the way the kidneys manage sodium. When the kidneys excrete more sodium, water excretion also rises. Most diuretics work by preventing sodium reabsorption in different parts of the renal tubules. Sometimes, two diuretics are combined because they work better together (synergistic effect). This happens because one part of the nephron can compensate for changes in sodium reabsorption in another part. By blocking multiple nephron sites, the overall effectiveness of diuresis increases significantly.

Loop diuretics

Loop diuretics work by blocking the sodium-potassium-chloride co-transporter in the thick ascending limb of the nephron. This transporter typically reabsorbs around 25% of the sodium load. By inhibiting this pump, loop diuretics significantly increase sodium concentration in the distal tubules, reduce the hypertonicity of the surrounding interstitial space, and decrease water reabsorption in the collecting duct. This results in both diuresis (Increased water excretion) and natriuresis (Increased sodium excretion).

Because the thick ascending limb plays a major role in sodium reabsorption, loop diuretics are among the most potent diuretics available. They also stimulate the kidneys to produce prostaglandins, enhancing their effects by increasing renal blood flow and redistributing

blood within the renal cortex. Their high efficacy stems from targeting a site with a large capacity for sodium reabsorption. However, their effectiveness decreases when renal function is compromised, such as in heart failure.

Eg: Furosemide, Bumetanide, Ethacrynic acid.

Thiazide diuretics

Thiazide diuretics, the most commonly prescribed type of diuretic, work by blocking the sodium-chloride transporter in the distal tubule. Since this transporter typically reabsorbs only about 5% of the filtered sodium, thiazides are less effective than loop diuretics in promoting diuresis (Increased urine output) and natriuresis (Sodium excretion). However, their diuretic effect is still strong enough to meet most therapeutic requirements. The effectiveness of Loop and thiazide diuretics increase sodium delivery to the distal part of the distal tubule, leading to greater potassium loss, which can potentially cause hypokalemia. This happens because the rise in sodium concentration in the distal tubule stimulates the aldosterone-sensitive sodium pump, promoting sodium reabsorption in exchange for potassium and hydrogen ions, which are then excreted in the urine. The increased loss of hydrogen ions can result in metabolic alkalosis.

Additionally, part of the potassium and hydrogen ion loss caused by these diuretics is due to the activation of the renin-angiotensin-aldosterone system. This activation occurs as a response to reduced blood volume and arterial pressure. Elevated aldosterone levels further enhance sodium reabsorption while increasing the excretion of potassium and hydrogen ions in the urine.

Eg: Hydrochlorothiazide, chlorthiazide.

Potassium-sparing diuretics

Potassium-sparing diuretics differ from loop and thiazide diuretics in that some do not directly affect sodium transport. Instead, certain drugs in this class work by blocking the effects of aldosterone (Aldosterone receptor antagonists or mineralocorticoid receptor antagonists, MRAs) in the distal part of the distal tubule. This inhibition increases sodium and water excretion through the urine.

These diuretics are called potassium-sparing because they do not cause hypokalemia like loop and thiazide diuretics. By blocking aldosterone-sensitive sodium reabsorption, less potassium and hydrogen ions are exchanged for sodium, resulting in reduced urinary loss of these ions.

Other potassium-sparing diuretics act by directly inhibiting sodium channels linked to the aldosterone-sensitive sodium pump, producing similar effects on potassium and hydrogen ions as aldosterone antagonists. Their action relies on renal prostaglandin production.

Due to their relatively mild effect on overall sodium balance, potassium-sparing diuretics are often combined with thiazide or loop diuretics to prevent hypokalemia.
Eg: Spironolactone, Amiloride, Triamterene.

Carbonic anhydrase inhibitors

Carbonic anhydrase inhibitors work by blocking the movement of bicarbonate from the proximal convoluted tubule into the interstitial space. This inhibition reduces sodium reabsorption at this site, leading to increased excretion of sodium, bicarbonate, and water in the urine. These diuretics are the least potent among diuretic classes and are rarely used for managing cardiovascular conditions.
Eg: Acetazolamide, Methazolamide.

Therapeutic uses

Hypertention: Diuretics are commonly used to manage hypertension, with around 90–95% of patients having primary or essential hypertension, where the exact cause is unknown. These drugs effectively lower blood pressure, especially when combined with a low-sodium diet. Their antihypertensive action works by reducing blood volume, lowering cardiac output, and, with prolonged use, decreasing systemic vascular resistance.

Thiazide diuretics, such as chlorthalidone, are recommended as first-line therapy for stage 1 hypertension due to their proven efficacy and long duration of action. They are particularly effective in elderly patients and those with salt-sensitive hypertension.

Potassium-sparing diuretics, like spironolactone and eplerenone, are useful for treating secondary hypertension caused by primary hyperaldosteronism. They also serve as adjuncts to thiazide therapy in primary hypertension, helping to prevent hypokalemia, a common side effect of thiazide use.

Additionally, diuretics can benefit hypertensive patients with heart failure, chronic kidney disease, and edema by promoting fluid excretion. Regular monitoring of electrolytes and renal function is essential during diuretic therapy to prevent complications and ensure safe, effective blood pressure management.

Heart failure: Heart failure activates the renin-angiotensin-aldosterone system, resulting in increased sodium and water retention by the kidneys. This leads to an expansion of blood volume, raising venous pressure and contributing to pulmonary and systemic edema. Diuretics play a key role in heart failure management by alleviating fluid overload, thereby reducing congestion and associated symptoms like shortness of breath (Dyspnea).

In addition to relieving edema, long-term diuretic use can lower afterload by promoting systemic vasodilation. This, in turn, improves ventricular ejection, enhancing overall cardiac performance and helping to manage heart failure more effectively.

Pulmonary and Systemic edema: Pulmonary and systemic edema result from increased capillary hydrostatic pressure, which is closely linked to elevated venous pressure. Diuretics help manage edema by reducing blood volume and venous pressure, thereby lowering capillary hydrostatic pressure. This decrease reduces net capillary fluid filtration, effectively minimizing tissue edema.

In cases of left ventricular failure, which can lead to life-threatening pulmonary edema, loop diuretics are commonly prescribed to prevent or alleviate fluid buildup in the lungs. Diuretics are also useful in treating leg edema caused by right-sided heart failure or venous insufficiency in the lower limbs.

Adverse side effects

Thiazide

- Hypokalemia
- Metabolic alkalosis
- Dehydration (Hypovolemia), leading to hypotension
- Hyponatremia
- Hyperglycemia in diabetics
- Hypercholesterolemia; hypertriglyceridemia
- Increased low-density lipoproteins
- Hyperuricemia (At low doses)
- Azotemia (In renal disease patients

Loop

- Hypokalemia

- Metabolic alkalosis
- Hypomagnesemia
- Hyperuricemia
- Dehydration (Hypovolemia), leading to hypotension
- Dose-related hearing loss (Ototoxicity)

K^+-sparing

- Hyperkalemia
- Metabolic acidosis
- Gynecomastia (Aldosterone antagonists)
- Gastric problems, Including peptic ulcer

CONCLUSION

Diuretics remain essential in clinical practice for managing hypertension, heart failure, and fluid overload conditions. Their effectiveness depends on the site of action within the nephron and the underlying condition being treated. Although they provide significant therapeutic benefits, diuretics can cause adverse effects, requiring regular monitoring of electrolytes and renal function. Combining different classes of diuretics can optimize therapeutic outcomes while reducing side effects. Continued research and individualized treatment approaches will further enhance the safety and efficacy of diuretic therapy in patient care.

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