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The Function of Diuretics in Current Medical Practice and Prospective Advancements

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Abstract

Diuretics have a rich history that spans several centuries, and this review aims to highlight their progression and clinical uses. We start by exploring kidney physiology, followed by a description of how diuretics function through symporters in the renal tubules. Different categories of diuretics are outlined, along with details of their specific actions. Next, we investigate the clinical use of diuretics in conditions, such as congestive heart failure and hypertension, as well as in some less prevalent but medically important conditions. The possible side effects of diuretics, along with their underlying causes, are also addressed. Frequent adverse effects, including hypokalemia and hyponatremia, are examined in depth, along with other electrolyte disturbances like hypomagnesemia. The role of diuretics in the management of chronic kidney disease is explored, along with updates on new guidelines in this field. A segment on diuretic misuse is included, given its growing recognition in clinical settings, emphasizing the often-tragic consequences of such abuse. Additionally, research is ongoing into the use of diuretics for diagnosing certain types of tubular renal acidosis. Lastly, some of the latest strategies for diuretic treatment are discussed, often stemming from advances in molecular biology, revealing new compounds that may soon enter future medication lists.

Keywords: Diuretics, urine concentration, thiazide diuretics, potassium sparing, hydrochlorothiazide

INTRODUCTION

Historical Perspective

The term diuretic has its origins in Greek, where “diu” means through and “ovpein” means to urinate [1]. Over the last forty years, multiple classes of diuretics, which are currently used in clinical practice, have been the preferred treatment for a range of cardiovascular and non-cardiovascular conditions [1]. Diuretics serve as the most recommended initial therapy for mild hypertension, and thiazide-type diuretics rank among the equally prioritized first-line treatment options, alongside beta-blockers, calcium channel blockers, and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers [2].

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The paintings found in the ruins of Pompeii have representations of grapes, ivy, olives and cherries – all of which have diuretic properties described in the writings of Pliny the Elder (AD 23–79). Diuretics are prescribed to promote diuresis and stimulate the loss of sodium and fluid in the urine. They can be used in patients who are clinically euvolemic to treat hypertension and are the mainstay of treatment in patients with conditions that cause edema and sodium retention. Diuretic overdose easily leads to volume depletion. Diuretics produce a negative sodium balance when they stimulate sodium excretion to the point where it exceeds intake. Diuretic-induced volume depletion is more likely to occur in the situations.

These conditions should be considered when a previously stable patient becomes volume depleted [3,4].

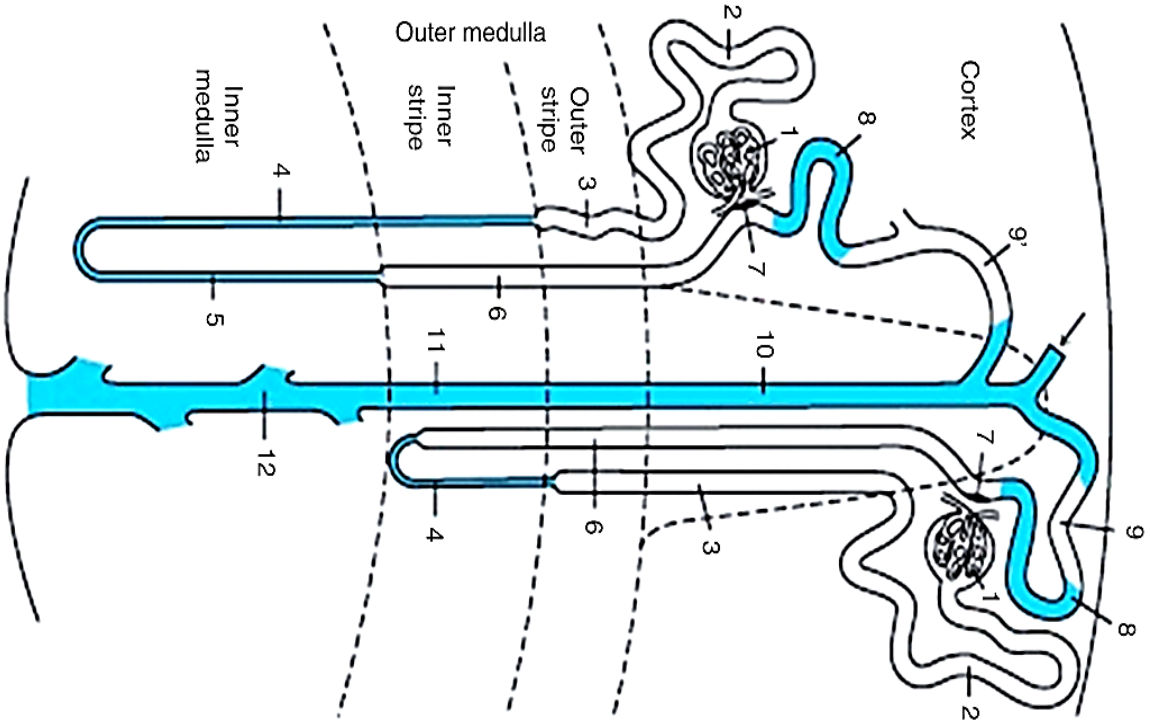

Figure 1. Structure of Nephron [4].

FUNCTIONAL ORGANIZATION OF NEPHRON

Proximal Tubules

The proximal tubules reabsorb half or more of the filtered sodium [5, 6]. Sodium reabsorption energizes the secondary active transport of numerous other solutes, including glucose, amino acids and bicarbonate, and normally alter sodium concentration in the lumen (Figure 1) [7].

Thin Limbs of Henle's Loop

It was not found that the thin limbs of the loop of Henle have active sodium transport in isolated rabbit perfused nephrons [8, 9]. There is passive sodium transport, however, at least in the thin ascending limb [10], and this has an important role in urinary concentration (Knepper & Burg, 1983) [11].

Thick Limbs of Henle's Loop

It transports the sodium very quickly.

PHYSIOLOGY OF KIDNEY

A normal human kidney receives approximately 1200 mL/min of blood flow. This indicates that 19% of the plasma that enters the kidneys undergoes filtration [12].

Urine formation begins from glomerular filtration of plasma. Blood enters the glomerulus through efferent arterioles. This capillary pressure is opposed by colloid osmotic pressure and capsule pressure [13].

MECHANISM OF DIURETICS

An increase in sodium excretion with accompanying anions and water can be achieved by increasing glomerular sodium filtration or by reducing sodium reabsorption from the nephron lumen. When diuresis occurs in an edematous patient, both mechanisms are often at work. Most primary diuretic agents probably have little or no direct influence on glomerular filtration, although this may be enhanced by other drugs, such as digoxin, that improve circulation to the kidney. Xanthine derivatives are often thought to act by increasing the glomerular filtration rate, and when given intravenously in man, theophylline may have some effect in this way [14].

Loop Diuretics

Their main place of action diuretics is the thick ascending limb of the loop of Henle, where the sodium-potassium chloride-2 reabsorption pump is inhibited. In addition, bumetanide and furosemide (frusemide) appear to have an additive effect in the proximal tubule, particularly when administered intravenously. In contrast, Lupinacci and Puschett (1988) showed that torasemide lacks a pro-tubular site of action. It is conceivable that the lack of proximal effect accounts for the diminution of kaliuresis reported to occur with torasemide [15,16].

Renal Tubular Site of Action of Loop Diuretics

Thick ascending limb of the loop of Henle: Na+ -K+ -2CI pump bumetanide furosemide piretanide torasemide Furosemide bumetanide.

Proximal Tubule

- *Thick ascending limb of Henle:* Chloride conductance (basolateral membrane).
- *Torasemide:* high dose (100 x that required for luminal effects) [17].

Potassium Sparing Diuretics

Physiological studies have identified the pivotal role of aldosterone in stimulating the reabsorption of N a+ in the distal tubule and the collecting duct in the exchange of K+ and H+. Derivatives of the steroid core of spirolactone was found to be active in animals with intact adrenals and inactive in those with adrenals-ectomy [18]. (Dyckner & Wmr, n.d.) Thus, it was assumed that the activity of these agents occurred by blocking aldosterone. As methods for studying the receptors and effects of steroids became available, these compounds were shown to block the aldosterone receptor competitively [19]. From this series of compounds, spironolactone was developed clinically [20–21].

In the distal nephron and collecting duct, sodium exchanges with K+ and H+. This process depends on the luminal entry of Na+ into the cell, a pathway blocked by amiloride and triamterene [22]. Exchange of sodium for K+ and H+ is also stimulated by aldosterone. Mineralocorticoid receptors in the cytoplasm of principal cells bind aldosterone; this hormone-receptor complex translocates to the cell nucleus, where protein synthesis, probably by Na+ pumps, is stimulated. 80·81 Spironolactone blocks the aldosterone receptor [23].

Thiazide Diuretics

Since the discovery of thiazide diuretics in 1957, which first offered the possibility of effective BP reduction, these drugs have been a main stay tool for the treatment of hypertension. Moreover, placebo-controlled clinical trials have clearly documented the benefit of thiazide diuretics, either alone or in combination with ␣ blockers, in reducing cardiovascular (CV) morbidity and mortality, a benefit like that obtained with other antihypertensive drugs. Broad drug categories, such as angiotensin-converting enzyme (ACE) inhibitors and calcium channel blockers, are discussed.

Cardiac output as determined by CO, rebreathing method failed significantly ($P < 0.05$) from a mean value of 6.4 L. per minute during the control period to 5.4 L. per minute 48 hours after starting hydrochlorothiazide [24].

In this population-based cohort study of 7891 older adults, patients who took thiazides for more than 1 year had a lower risk of hip fracture than those who did not take thiazides (hazard ratio, 0.46 [95% CI, 0.21 to 0.96]). Within 4 months of stopping thiazides, the risk of hip fracture returned to the pre-treatment value .

Carbonic Anhydrase Inhibitors

Carbonic anhydrases are commonly found zinc enzymes located in archaea and eubacteria, algae, green plants, and animals. In these organisms, carbonic anhydrases are encoded by three separate and evolutionarily distinct gene families: α-CA, β-CA, and γ-CA families, respectively.

These enzymes act as highly effective catalysts for the reversible conversion of CO2 to bicarbonate; α-CA is particularly versatile, as it can also facilitate other hydrolytic reactions [25].

CLINICAL APPLICATIONS OF DIURETICS

Hypertension

Improved urinary excretion of Na+ ions and water of diuretics is accompanied by a reduction in plasma volume and cardiac output. However, reflex activation of the renin-angiotensin-aldosterone system can lead to vasoconstriction of systemic arterial resistance vessels and compensate for the fall in blood pressure [26].

Liver Cirrhosis

The earliest studies primarily used loop diuretics to treat cirrhotic patients with ascites. Estimates of fluid mobilization with diuretics suggested that a maximum of 1 L/day of ascites could be mobilized without substantial complications, such as decreased renal function., there have even been recommendations that patients with ascitic cirrhosis should not be diuresed at all because of the potential deterioration of renal function that correlates with mortality. A randomized trial, however, showed that more gradual diuresis with natriuretic doses of spironolactone could lead to resolution of ascites in 3 to 4 weeks [27].

Adverse Effect of Diuretics

Thiazide diuretics are recognized for inducing hypokalemia, which can result in arrhythmias. This reduction in potassium level leads to an increase in blood glucose. Restoring potassium levels can reverse this glucose intolerance. Loop diuretics can cause interstitial nephritis and skin reactions. Caution should be exercised with loop diuretics, particularly at high doses, as they may lead to temporary ototoxicity. The administration of loop diuretics is also correlational with hypokalemia, posing risks of cardiac arrhythmias and potential mortality [28].

Modern Trends in Development of Diuretics

Recently, pharmaceutical researchers have been striving to create new medications with improved pharmacological characteristics. High-throughput screening, enhanced protein structure analysis, and modern techniques in chemical modification have provided promising opportunities for finding new agents suitable for preclinical and clinical evaluation. Various medicinal chemistry strategies have led to the discovery of small molecule compounds demonstrating diuretic properties over the last decade, which serve as intriguing drug candidates. Classes, such as vasopressin receptor antagonists, SGLT2 inhibitors, urea transporter inhibitors, aquaporin antagonists, adenosine receptor antagonists, natriuretic peptide receptor agonists, ROMK, WNK-SPAK inhibitors, and pendrin inhibitors fall under the categories of natriuretics/aquaretics/osmotic diuretics [29-30].

CONCLUSIONS

A newly identified class of diuretics presents an exciting challenge for medical research. These are referred to as AQP modulators and show potential for commercial use, as a patent application has recently been submitted for the first of its kind, AqB013. Physiologists have long speculated about the presence of “gates” that would facilitate rapid water reabsorption by the cells within the renal tubules. AQP1 is primarily found in the proximal tubule and the thin descending limb of the loop of Henle,

while AQP2 is present in the principal cells of the collecting duct, where it moves between intracellular vesicles and the apical membranes in response to vasopressin. Increased activity of AQP2 contributes to the pathophysiology of conditions, like cirrhosis, heart failure, and nephrotic syndrome, which are managed with diuretics. Genetic mutations in the AQP2 gene can lead to nephrogenic diabetes insipidus. Mouse knockout models have been created to investigate the modulation of AQP function and expression. Verkman's analysis indicates that mouse phenotypic data suggest the potential for AQP expression/function modulators to have wide-ranging clinical implications in diagnosing glaucoma, obesity, cerebral edema, and cancer.

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