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REVIEW ARTICLE

Terapi Diuretik: Furosemid dan Tiazid

Josephine Audi[1], Inda Meirani Herawita Br Sinaga[2]

1. Medical Education Study Program, Faculty of Medicine, Methodist University of Indonesia
2. Department of Pharmacology, Faculty of Medicine, Universitas Methodist Indonesia, Medan, Indonesia.

Correspondence:
josephineaudi11@gmail.com

ABSTRACT

Background: Diuretics are a primary pharmacological class used to regulate kidney function in the excretion of water and electrolytes, leading to increased urine production and volume. The mechanism involves the suppression of receptors responsible for the reabsorption of sodium (Na+)—the primary extracellular cation—within the renal tubules. This inhibition increases tubular osmolality, thereby suppressing water reabsorption.

Mechanism of Action: This study explores two major classes: Loop diuretics and Thiazides. Loop diuretics exert their effect by inhibiting the Na+−K+−2Cl− (NKCC2) cotransporter on the apical membrane of the thick ascending limb of the loop of Henle. In contrast, Thiazides inhibit sodium-chloride (Na/Cl) channels in the distal convoluted tubules of the nephron.

Synergistic Effect: Clinical evidence suggests that the addition of Thiazides can potentiate the efficacy of Loop diuretics. This synergy occurs by inhibiting sodium reabsorption in the distal tubule and blocking the compensatory responses—such as distal nephron hypertrophy—that typically arise from long-term exposure to Loop diuretics.

Conclusion: Understanding the distinct and combined mechanisms of Furosemide and Thiazides is essential for optimizing fluid management and overcoming diuretic resistance in clinical practice.

Keywords: Diuretics, Furosemide, Thiazide, Renal Tubules, Electrolyte Excretion.

INTRODUCTION

Diuresis is essential for various clinical conditions requiring the removal of fluid accumulation from the third space. Diuretics are classified into several groups: thiazides, loop diuretics, potassium-sparing diuretics, carbonic anhydrase inhibitors, and osmotic diuretics. Loop diuretics remain the mainstay therapy for symptomatic heart failure, with furosemide being the most frequently utilized agent.

Thiazides are considered the primary choice for hypertension according to the latest Cochrane review. Specifically, chlorthalidone, which possesses a longer duration of action and half-life at low doses, is recognized as the superior first-line agent among all antihypertensive drugs by the 2017 American College of Cardiology (ACC) guidelines. It has been significantly proven to reduce the risk of cardiovascular events compared to other agents.1

The combination of loop diuretics with thiazides, which act on the distal tubule, is believed to prevent sodium retention that occurs following loop diuretic treatment. Furosemide is often used due to its high efficacy in symptomatic heart failure. The supplemental administration of thiazides can potentiate the effects of loop diuretics by inhibiting sodium reabsorption in the distal tubule and blocking the compensatory response resulting from long-term loop diuretic exposure.1,2

B. Administration of Furosemide

Furosemide can be administered either orally or intravenously. Oral formulations are available in tablet and syrup forms. Tablets are available in dosage variations of 20 mg, 40 mg, and 80 mg. The syrup is available in concentrations of 8 mg/mL and 10 mg/dL. The intravenous (IV) formulation is available at a concentration of 10 mg/dL. 4

Furosemide Dosages by Indication

Indication	Daily Dose; Maximum Dose
Chronic Heart Failure	40–240 mg oral; 600 mg oral
SIADH	20 mg; 40 mg
Hypermagnesemia	20–40 mg IV
Hyperkalemia	40–80 mg IV
Acute Pulmonary Edema	40 mg IV over 1–2 minutes, increased to 80 mg if no response
Secondary Hypertension	20–80 mg; 160 mg
Ascites in Cirrhosis	20 mg; 160 mg

A. Impact and Mechanism of Furosemide

Loop diuretics (furosemide) function by inhibiting the NKCC2 transporters in the kidneys, located on the luminal (apical) membrane of the Thick Ascending Limb (TAL) of the loop of Henle. Loop diuretics act as anions (negatively charged ions) that block the chloride-binding site of the NKCC2 transport protein. By inhibiting NKCC2 in the TAL, these diuretics prevent the reabsorption of sodium (Na^+), potassium (K^+), and chloride (Cl^-), thereby reducing the interstitial tonicity of the renal medulla and interfering with the urinary concentration mechanism.

Furthermore, the TAL's function in diluting tubular fluid is compromised, resulting in increased sodium delivery to the distal tubule. Normally, elevated sodium levels would trigger the Tubuloglomerular Feedback (TGF) mechanism, which reduces the Glomerular Filtration Rate (GFR) by constricting the afferent glomerular arterioles. However, because macula densa cells also utilize NKCC2, loop diuretics diminish the ability of these cells to sense salt levels, effectively deactivating the TGF. Additionally, the salt depletion or fluid volume reduction caused by diuretic use can trigger renin release, activating the Renin-Angiotensin-Aldosterone System (RAAS), which helps maintain GFR by increasing blood pressure.1

Toxicity and Adverse Effects: Toxicity from loop diuretics may manifest as electrolyte imbalances, such as hyponatremia, hypokalemia, and hypocalcemia, as well as acid-base disturbances like hypochloremic alkalosis.3 Reversible ototoxicity (manifested as sensorineural hearing loss and tinnitus) is a specific adverse effect of loop diuretics, caused by ischemia in the *stria vascularis* and the inhibition of NKCC1 channels located there. Tinnitus is most common when large bolus doses are administered, leading to high peak serum concentrations.1 Loop diuretics are classified as Pregnancy Grade C. When considering administration, it is crucial to weigh the risks and benefits, particularly the potential risk of kernicterus in newborns.3

B. Comparison with Thiazides

Thiazide diuretics are a class of drugs that inhibit the sodium-chloride (Na/Cl) symporter in the distal convoluted tubule of the nephron, thereby increasing sodium excretion (natriuresis) and water excretion (diuresis). When the distal tubule is blocked, less sodium enters the cells, reducing the activity of the sodium-potassium (Na/K) pump. The increased flow of sodium to the collecting duct results in more sodium being reabsorbed in exchange for increased secretion of potassium (K+) and hydrogen (H+) ions into the urine.5

Thiazide diuretics, such as chlorthalidone and indapamide, are more effective at lowering blood pressure in patients with primary hypertension and normal renal function compared to loop diuretics. This is attributed to their longer duration of action. Loop diuretics, such as furosemide and bumetanide, are short-acting (less than six hours), which can limit their antihypertensive efficacy. Once the diuretic effect wanes, the body activates the RAAS, leading to post-diuretic sodium retention.6

Thiazide diuretics have a lower affinity for competing with organic acids compared to loop diuretics. Consequently, thiazides are considered less effective in patients with a GFR below 30 mL/min. Since fluid retention is a primary factor in elevated blood pressure within Chronic Kidney Disease (CKD), loop diuretics are typically preferred as the antihypertensive treatment for this population.6

CONCLUSION

Combination diuretic therapy, specifically the addition of thiazide diuretics to loop diuretics, is an effective strategy for managing refractory fluid overload in heart failure patients. The method of **sequential nephron blockade**, which targets different segments of the nephron, can significantly enhance urinary and sodium excretion, thereby alleviating clinical symptoms. This combination therapy proves more effective in promoting diuresis and improving treatment outcomes in patients who show an inadequate response to monotherapy.

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