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CLINICAL AND PHARMACOLOGICAL CHARACTERISTICS OF LOOP DIURETICS AND CURRENT APPROACHES TO THEIR RATIONAL USE

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АНОТАЦІЯ

Introduction. This issue is relevant because it is necessary to integrate theoretical and clinical understanding of loop diuretics with the challenges of modern medicine. The prescription of drugs such as furosemide, torasemide, and bumetanide is often based on stereotypes rather than on individual patient characteristics, despite the fact that they have been widely used for decades. This leads to widespread diuretic resistance, frequent hospitalizations due to exacerbations of chronic heart failure, and the emergence of predictable complications such as severe hypokalemia or renal dysfunction. In light of the epidemic of cardiovascular and metabolic diseases, optimizing the most common therapeutic interventions is a key priority for improving patients' quality of life and the efficient use of healthcare resources. New data are challenging traditional approaches, highlighting the current relevance of this issue. According to recent studies, pharmacokinetic variability (e.g., unpredictable bioavailability of furosemide) and pathophysiologically grounded approaches to overcoming resistance (e.g., sequential nephron blockade) are vital. To achieve this, it is necessary to move away from standard regimens and instead use individualized strategies that take into account the specific diagnosis, renal status, hypoalbuminemia, and other factors. Thus, systematizing this knowledge through comprehensive work not only bridges the gap between cutting-edge science and clinical practice but also serves as the foundation for developing local clinical protocols and educational programs aimed at enhancing the professional competence of physicians and pharmacists.

The aim of this theoretical study is to examine the clinical and pharmacological properties of loop diuretics, as well as to develop, based on current data, evidence-based strategies for their rational use in various clinical situations.

Materials and methods. An analytical review of current scientific publications, pharmacological studies, and clinical guidelines regarding the use of furosemide, bumetanide, and torasemide was conducted. The literature search was performed in the PubMed, Scopus, and Web of Science databases using relevant keywords. The obtained data were synthesized using methods of comparative and systematic analysis.

Results. The human body functions as a complex system, and maintaining water and electrolyte balance is crucial for the normal functioning of all organs. The kidneys play a key role in regulating fluid volume and electrolyte levels, ensuring a stable internal environment.

The primary molecular target of loop diuretics is the Na/K/2Cl cotransporter (NKCC2), which is located in the apical membrane of the epithelial cells of the thick ascending limb of Henle's loop. Under normal conditions, it facilitates the reabsorption of sodium, potassium and chloride from primary urine and maintains the osmotic gradient necessary for urine concentration and the regulation of water and electrolyte balance [1, 2]. Inhibition of this cotransporter also leads to increased excretion of calcium and magnesium. The most clinically significant consequence of this phenomenon is the development of hypokalaemia, which may be accompanied by muscle weakness and cardiac arrhythmias. The loss of calcium and magnesium also adversely affects the functional state of the muscular and skeletal systems, necessitating regular monitoring of electrolytes and timely correction of any imbalances during treatment [3, 4].

The action of loop diuretics is determined by their properties, such as molecular structure, lipophilicity, and bioavailability. For example, furosemide, bumetanide, and torasemide work slightly differently because they affect cotransporter NKCC2 in different ways. As a result, both the onset of diuresis and its intensity vary. If a substance is more lipophilic, it penetrates cells more quickly and, consequently, begins to act sooner. At the same time, bioavailability influences how long and how pronounced the effect is after oral administration [4, 5].

Loop diuretics act not only through NKCC2. They are also associated with the formation of prostaglandins in the kidneys. As a result, blood vessels dilate slightly and blood flow improves. Therefore, the kidneys filter blood more effectively, even if there was a previous issue, such as heart failure. This helps the body excrete more fluid and electrolytes, and the diuretic effect becomes more pronounced. Additionally, prostaglandins support nephron function and help maintain electrolyte balance. All of this is necessary for the normal functioning of the kidneys and the body as a whole [6, 7].

Various loop diuretics, such as furosemide, bumetanide, and torasemide, differ slightly in their structure. These differences affect how quickly the drugs are absorbed in the gastrointestinal tract and when their effects begin. This also affects the duration of the effect. Each drug acts slightly differently in the body. It interacts with blood proteins, is distributed throughout the tissues, and is processed by the liver. This is why a doctor can select the appropriate dose and dosing regimen to achieve the optimal therapeutic effect and minimise adverse reactions, due to differences in the pharmacological properties of loop diuretics (Table 1) [4, 5].

Furosemide is absorbed by the body to varying degrees – ranging from 10% to 100%. This is influenced by what we eat and the condition of the stomach and intestines. Because of this, its effect can sometimes be unpredictable. Bumetanide and torasemide are absorbed much better – about 80-90% – so their effect is more stable. In practice, this is important: if you need to quickly reduce swelling, furosemide can help, but its effect is less predictable. For long-term therapy, it is

better to use bumetanide or torasemide, as they work predictably and consistently [3].

After absorption into the systemic circulation, loop diuretics bind extensively to plasma proteins, primarily to albumin. This pharmacokinetic feature limits their distribution in tissues and results in a relatively small volume of distribution. The clinical significance of high protein binding lies in the fact that when plasma albumin concentrations are reduced – particularly in nephrotic syndrome, liver disease, or systemic inflammatory processes – the proportion of the free, pharmacologically active fraction of the drug increases. This can lead both to an increase in the diuretic effect and to an increased risk of adverse reactions, primarily electrolyte imbalances and signs of toxicity. Consequently, in patients with hypoalbuminemia or concomitant pathological conditions, individual dosage adjustment is necessary to enhance the safety and efficacy of therapy [8].

Bumetanide and torasemide are almost entirely metabolized in the liver, so they work consistently even in people with impaired kidney function. Furosemide works a little differently: it is partially excreted by the kidneys and partially metabolized in the liver. Because of this, its effect may be less predictable, especially if a person has problems with both the kidneys and the liver. Understanding how these drugs are broken down and excreted helps doctors choose the right dose, decide how often to administer the medication, and reduce the risk of side effects [1].

The half-life ($t_{1/2}$) of loop diuretics indicates how long the drug remains active in the body and when a repeat dose is needed. Furosemide has a short $t_{1/2}$ approximately 1.5-2 hours. Because of this, its effect wears off quickly, so patients often need to take it several times a day. This is important for people with heart failure or edema. Bumetanide and torasemide last longer, with a $t_{1/2}$ of about 3-4 hours. As a result, the effect is more prolonged, and the medication can be taken less frequently. Knowing this helps doctors choose the right drug and properly schedule dosing for each patient [8].

If the kidneys are not functioning properly, furosemide remains in the body longer and can accumulate. This can lead to excessive urination or imbalances in blood salt levels. Torasemide and bumetanide do not behave this way – they are broken down in the liver and work consistently even when there are kidney problems. This makes it easier for doctors to select the correct dose and ensure safe treatment [9, 10].

Threshold concentration

This is the minimum level of the drug in plasma or the renal tubules required for a clinically significant diuretic effect to occur. Doses below the threshold remain pharmacologically ineffective. Adherence to this principle is particularly important in the treatment of acute edema and heart failure [11].

If a large amount of loop diuretics accumulates in the blood and renal tubules, the proteins responsible for their excretion cannot work faster – they become «saturated». Therefore, increasing the dose does not produce a stronger diuretic effect. Too high a dose can cause dehydration or a drop in potassium, sodium, and other

electrolyte levels, which harms the heart and kidneys. Doctors adjust the dose gradually to achieve the desired effect without harming the patient. This is especially important for people with heart failure or kidney problems, where maintaining fluid balance is critical [12].

People respond differently to loop diuretics. This depends on age, kidney function, blood protein levels, and other medical conditions. In people with kidney problems, the diuretic may only be effective at a higher dose. If a doctor takes these factors into account, they can prescribe a dose that is both effective and safe, with minimal risk of side effects such as dehydration or electrolyte imbalances [13].

The effect of loop diuretics depends on how quickly the medication reaches the kidneys. In the renal tubules they affect proteins that regulate urine production. If the drug reaches the kidneys slowly, its effect is reduced, even if there is enough of it in the blood. This happens with low blood flow to the kidneys, heart failure, fluid deficiency, or when taking medications that reduce the diuretic effect. In such cases, the standard dose may be ineffective. The doctor may change the route of administration or the dose to achieve the desired effect and avoid dehydration and electrolyte imbalances [6].

Loop diuretics are characterized by a rapid onset of pharmacological action, which makes them particularly effective in clinical settings. At the same time, the duration of the diuretic effect is limited and depends on the drug's half-life. Consequently, after a single dose, the concentration of the drug may fall below the threshold level, leading to reduced efficacy.

In light of these characteristics, it is essential to carefully determine the dosing frequency. The administration of repeated or divided doses helps maintain the pharmacological concentration above the required threshold throughout the 24-hour cycle, ensuring a continuous diuretic effect. This approach is particularly relevant for people suffering from chronic edema or congestive heart failure, which requires careful monitoring of fluid balance [14].

Interactions with other medications

Loop diuretics can interact with other medications. If a drug "competes" for excretion in the kidneys or binds strongly to blood proteins, this can alter the amount of diuretic reaching the kidneys and its effect. This is especially true for nonsteroidal anti-inflammatory drugs – they can prevent the diuretic from reaching the renal tubules. As a result, furosemide or other diuretics are less effective at inhibiting the NKCC2 transport protein,

and the diuretic effect weakens. As a result, fluid is retained, swelling worsens, and blood pressure may rise. Knowing this, the doctor can properly adjust the dose, modify the treatment, or choose a different medication to ensure the therapy is safe and effective [9, 10].

The efficacy of loop diuretics may vary when used concomitantly with other medications. In particular, non-steroidal anti-inflammatory drugs, thiazide diuretics, and renin-angiotensin-aldosterone system inhibitors can affect pharmacodynamics by shifting the dose-response curve or increasing the threshold concentration. As a result, the diuretic response may be reduced, even at standard dosages. Therefore, consideration of potential drug interactions is essential for the proper selection of therapeutic strategies, especially in patients with refractory edema [9].

Diuretic resistance is a physiological condition in which loop diuretics fail to elicit the expected diuretic response, even when the patient adheres to the prescribed doses and follows the appropriate treatment protocol. In other words, the body does not exhibit the expected pharmacological response to the medication under standard physiological conditions.

This phenomenon can arise for various reasons: for example, the diuretic may fail to reach the intended site of action in the renal system at the required concentration, or its efficacy may be reduced as a result of the body's compensatory mechanisms, which attempt to maintain water-electrolyte homeostasis. In addition, human pharmacokinetic and pharmacodynamic properties, including renal function, plasma protein concentrations, and the presence of any comorbidities, significantly influence the therapeutic efficacy of pharmacological agents. Understanding this is crucial for the clinician: it facilitates timely dosage adjustments, the selection of diuretic combinations, or the exploration of alternative strategies to maintain fluid volume regulation and mitigate potential complications [14].

Diuretic resistance is common among patients with heart failure (especially in the chronic form) and in patients with renal dysfunction or comorbid conditions.

Various studies show that up to 20-30% of patients with severe heart failure have a significantly reduced response to diuretics [15, 16].

The role of renal insufficiency

- In patients with chronic renal insufficiency (CRI), a decrease in glomerular filtration rate (GFR) and impaired tubular secretion reduce the delivery of loop diuretics to the site of pharmacological action in the nephron.

Table 1

Pharmacological characteristics of loop diuretics

Medicine	Bioavailability	Onset of action of the drug	Duration of action of the drug	Features
Furosemide	Approximately 50–60%	Fast	4–6 hours	Most commonly used, effective in edema and heart failure
Bumetanide	About 80–90%	Very fast	4–6 hours	More potent at lower doses compared to furosemide
Torsemide	80–100%	Relatively fast	8–12 hours	Longer duration of action and more stable effect

- Consequently, even with adequate plasma concentrations of the drug, the availability of the diuretic in the tubules remains insufficient, leading to a weakening or loss of the diuretic effect.

- Pathophysiologically, this is explained by impaired intact transport of the drug from the blood into the nephron lumen, as well as tubular adaptation to prolonged ion loading, which reduces sensitivity to the diuretic's action [3].

In cases of cardiac or renal pathology, the body often activates compensatory mechanisms that maintain water-electrolyte balance. One of the key mechanisms is increased activity of the renin-angiotensin-aldosterone system (RAAS) and the sympathetic nervous system. These mechanisms cause the kidneys to reabsorb more sodium and water, which effectively counteracts the diuretic effect of loop diuretics.

In clinical practice, this manifests as a reduction in the efficacy of standard doses of diuretics: even when blood levels of the drug are sufficient, urine output may remain low. This neurohormonal compensation is one of the main causes of diuretic resistance, particularly in patients with chronic heart failure or renal dysfunction. Understanding this phenomenon helps the physician accurately assess the efficacy of therapy and, if necessary, adjust the treatment regimen – for example, by selecting drug combinations or additionally targeting the RAAS to improve the response to treatment [17].

Certain medications can reduce the efficacy of loop diuretics. These include nonsteroidal anti-inflammatory drugs that inhibit prostaglandin synthesis, RAAS inhibitors, and drugs that compete for tubular secretion. These interactions can diminish the diuretic response, even at standard doses. In clinical practice, it is important to consider such interactions to adjust treatment regimens and maintain adequate diuretic effects in patients with cardiac or renal disease [18].

Hemodynamic disturbances, such as reduced cardiac output, lead to decreased renal perfusion, which impairs the delivery of loop diuretics to the nephrons and reduces their efficacy. In addition, metabolic factors such as hypoalbuminemia, acidosis, or hypertension can alter the drug's distribution in the body and its pharmacodynamic effects. In clinical practice, this means that patients with such conditions may exhibit a diminished response to standard therapy, requiring an individualized dosing approach and careful monitoring of the effect [3].

In patients with congestive heart failure, the absorption of loop diuretics in the gastrointestinal tract may be impaired due to edema of the intestinal mucosa and changes in gastrointestinal motility. This can reduce the absorption of oral medications, preventing the achievement of full therapeutic blood concentrations. Switching to intravenous administration of the drug allows the doctor to maintain a constant level of the diuretic in the blood, which promotes stable urine output. This approach is particularly beneficial for patients in whom oral formulations have a weak effect, as it allows for an improved therapeutic response and reduces the risk of treatment failure [18].

In patients who exhibit significant resistance to loop diuretics, the administration of bolus doses can lead to fluctuations in plasma concentrations of the drug, thereby reducing the efficacy of the diuretic effect and stimulating compensatory neurohormonal pathways, such as the renin-angiotensin-aldosterone system (RAAS). The use of continuous intravenous infusion helps maintain stable diuretic concentrations, thereby minimizing fluctuations in serum levels and achieving a more consistent diuretic response. This approach not only enhances therapeutic efficacy but also mitigates the risk of complications that may arise from an inadequate therapeutic response. In clinical settings, the use of continuous infusion is particularly justified in severe cases of congestive heart failure, when conventional administration methods do not yield the expected therapeutic results [19].

Regulating sodium intake is a key aspect of effective treatment with loop diuretics. Excess dietary sodium causes increased sodium reabsorption in the distal segments of the nephron, thereby significantly reducing the effectiveness of diuretics and potentially promoting the accumulation of excess fluid in the body. In clinical practice, strict adherence to dietary sodium-restriction guidelines helps maintain a stable diuretic response, prevent the progression of edema, and reduce the risk of complications associated with congestive heart failure. In addition, sodium control enhances the effectiveness of drug therapy, allowing the physician to achieve a more predictable and safer treatment outcome [19].

Monitoring electrolyte balance and renal function is of paramount importance during treatment with loop diuretics. Assessing sodium, potassium, and creatinine levels in conjunction with estimating glomerular filtration rate facilitates the timely detection of treatment-related adverse changes, particularly those involving electrolyte imbalance or impaired renal function. The results obtained are used to adjust the dose and refine the treatment regimen, taking into account the patient's clinical condition. In clinical practice, this approach helps reduce the risk of complications and ensure a stable response to loop diuretic monotherapy [20].

In addition to mechanisms related to reduced drug delivery to the site of action or activation of neurohormonal systems, long-term use of loop diuretics may lead to adaptive changes in the structure and function of the nephron. Such changes include hypertrophy of cells in the distal segments of the nephron and increased activity of sodium reabsorption mechanisms after the diuretic's effect has ceased. This phenomenon, known as «post-diuretic sodium retention», involves a compensatory increase in sodium reabsorption in the distal segments of the nephron following a decrease in the diuretic's blood concentration, which partially offsets the previous diuretic effect. Understanding this process allows for better prediction of the clinical response to treatment, particularly with long-term use of loop diuretics and in patients with recurrent episodes of edema [21].

The action of loop diuretics depends on how the drug is absorbed, distributed, and excreted from the

body. These processes may vary among patients. For example, reduced albumin levels alter the drug's binding to blood proteins. Other medications, particularly those excreted via the renal tubules, may also influence the effect.

In cases of edema or dehydration, the volume of distribution changes, which can also affect the drug's concentration. Therefore, during treatment, potential interactions and the patient's condition are taken into account, and the dose is adjusted as needed [21].

In conjunction with dose adjustments or changes in the route of administration, the method of assessing urinary sodium excretion is increasingly being used to monitor the efficacy of loop diuretics. Measuring natriuresis allows for an objective assessment of the diuretic response, independent of plasma drug concentration and clinical manifestations of fluid retention.

This approach allows for the timely detection of an inadequate response to treatment and real-time adjustment of the therapy regimen (specifically, the dose or frequency of administration), preventing excessive dose increases that could lead to electrolyte disturbances or dehydration. In patients with acute heart failure, the use of protocols focused on natriuresis increases the accuracy and predictability of the diuretic response [3].

When only one diuretic is used, the effect is sometimes weak. This is because the kidneys can «compensate» for sodium loss and begin to reabsorb more of it in other parts of the nephron.

Therefore, in such situations, doctors add another drug that acts at a different site. For example, a loop diuretic is often combined with a thiazide or a potassium-sparing diuretic. This enhances the diuretic effect.

This treatment option is typically used for edema or heart failure, when excess fluid needs to be eliminated more quickly. However, it is important to monitor laboratory tests, especially electrolyte levels, as potassium and sodium levels may decrease [3].

In patients who respond poorly to monotherapy with loop diuretics, a combination with thiazide or thiazide-like diuretics is often used. This allows for the blockade of additional segments of the nephron, reducing compensatory sodium reabsorption in the distal tubules, which improves fluid excretion and plasma volume control. Close monitoring of electrolytes and renal function is essential, as combination therapy may increase the risk of potassium and sodium imbalance. Physicians primarily use this approach in patients with heart failure or severe renal dysfunction, where monotherapy does not produce the expected effect [22].

In clinical practice, patients with acute heart failure are often prescribed a combination of diuretics from different classes to enhance the diuretic effect. This combination allows for the blockade of natriuretic mechanisms at different sites of the nephron, which is particularly important when standard monotherapy with loop diuretics does not provide sufficient reduction in fluid volume. The use of sequential blockade facilitates faster control of edema and a reduction in venous pressure, which improves the patient's hemodynamic status and overall clinical prognosis [23].

Combination diuretic therapy is used to enhance the efficacy of diuretics in patients with heart failure, particularly in cases where there is an inadequate response to monotherapy. This approach promotes rapid relief of congestive symptoms and improves clinical status in the short term. However, its impact on long-term prognosis remains uncertain. Existing research findings do not provide conclusive evidence of reduced mortality or the frequency of rehospitalizations associated with concomitant diuretic use. Therapeutic outcomes depend on the severity of heart failure, renal function, and the presence of comorbid conditions. Furthermore, aggressive diuresis may be associated with electrolyte imbalances and changes in renal function, requiring constant monitoring. Therefore, the initiation of combination therapy should be based on a comprehensive assessment of the patient's clinical condition and accompanied by strict clinical and laboratory monitoring [23].

The concurrent use of multiple diuretics may be associated with disturbances in water and electrolyte balance. This is because the drugs act on different parts of the nephron and potentiate each other's effects. Most commonly, this therapy is associated with a decrease in blood potassium and sodium levels. Such changes may develop gradually, but sometimes occur rapidly, especially if diuresis is pronounced. These changes can cause clinical manifestations ranging from general weakness and cardiac arrhythmias to neurological symptoms in cases of a significant decrease in sodium levels.

In addition to electrolyte shifts, the combined use of diuretics may affect renal function. A decrease in intravascular volume and changes in renal tissue perfusion sometimes lead to elevated creatinine levels and a decrease in glomerular filtration rate. The risk of such complications increases in elderly patients, those with pre-existing renal impairment, and in the presence of concomitant therapy that affects renal hemodynamics.

Therefore, the use of a combined diuretic regimen requires caution. Regular laboratory monitoring of electrolyte levels, creatinine, and other indicators of renal function is a prerequisite for safe treatment. Timely detection of abnormalities allows for dose adjustment or temporary modification of the therapeutic approach, thereby reducing the risk of serious complications [24].

When selecting combination diuretics, it is essential to consider their specific mechanisms of action in the body and the functional status of the kidneys. The duration of the drug's action, its route of elimination, and the potential for accumulation in cases of reduced glomerular filtration rate are all important factors. In practice, a thiazide or thiazide-like agent is often added to a loop diuretic if the response to monotherapy is insufficient. With reduced GFR (glomerular filtration rate), metolazone or chlorthalidone may be used, as they remain effective even with moderate renal impairment.

However, such a combination requires caution. The risk of electrolyte disturbances and excessive fluid loss increases; therefore, treatment is conducted with regular monitoring of laboratory parameters and dose adjustments depending on the clinical situation [24].

Despite the available clinical data, the optimal regimens for combination diuretic therapy remain poorly defined. Further studies are needed to compare different drug combinations, doses, and treatment durations, taking into account the characteristics of specific patient groups. It is important to evaluate the efficacy of therapy in people with varying degrees of heart failure, renal impairment, and comorbidities to ensure safe and predictable treatment outcomes. An individualized approach to initiating combination therapy allows for the selection of pharmacological agents and adjustment of dosing regimens based on clinical and laboratory parameters, which subsequently enhances treatment efficacy and mitigates the likelihood of adverse effects. An effective strategy for individualizing treatment not only facilitates symptom management in the short term but also enhances the safety and predictability of long-term therapeutic outcomes [22]. The mechanism of action of individual groups of diuretics is shown in Table 2.

Loop diuretics, including furosemide, torasemide, and bumetanide, act in the thick ascending limb of Henle's loop, where they inhibit the $\text{Na}^+\text{-K}^+\text{-2Cl}^-$ cotransporter. This leads to increased excretion of sodium and chloride in the urine. In response, potassium loss increases in the distal tubules, which is associated with the activation of sodium-potassium exchange and the effects of aldosterone.

As a result, blood potassium levels may decrease. This manifests as muscle weakness, cramps, a tingling sensation, as well as heart rhythm disturbances, including arrhythmias. The risk of such changes increases with long-term use, high doses, or when combined with other medications that also deplete potassium (e.g., corticosteroids or aminoglycosides).

Therefore, it is important to regularly monitor blood potassium levels during treatment. If necessary, the doctor may prescribe potassium supplements or recommend dietary changes to avoid complications [25].

Long-term use of loop diuretics can lead not only to potassium loss but also to a decrease in blood sodium and chloride levels. Due to increased fluid excretion, the body loses these electrolytes, which can cause hyponatremia and hypochloremia.

Hyponatremia typically presents with general weakness, dizziness, headache, and altered consciousness. In more severe cases, seizures or even coma may occur. Hypochloremia is often less noticeable, but it can lead to metabolic alkalosis and further disrupt electrolyte balance.

The risk of such complications increases with long-term treatment, high doses, in elderly patients, or when combined with other medications that also lower sodium levels, such as thiazide diuretics.

To avoid these problems, it is important to regularly monitor blood sodium and chloride levels during therapy. If necessary, fluid volume is corrected and appropriate electrolytes are administered [1].

Magnesium is an essential electrolyte for the optimal functioning of both the cardiovascular and neuromuscular systems. Long-term use of loop diuretics leads to increased renal excretion of magnesium, which can potentially cause hypomagnesemia. This deficiency often goes undetected because its clinical manifestations may be subtle during the early stages. Nevertheless, when combined with hypokalemia, hypomagnesemia significantly increases the likelihood of cardiac arrhythmias, including ventricular arrhythmias, and further exacerbates muscle spasms, cramps, and weakness. The elderly and individuals with concomitant renal disorders or those on polypharmacy are particularly susceptible. To effectively prevent adverse outcomes, it is advisable to conduct regular assessments of serum magnesium levels and, if indicated, implement corrective measures through magnesium supplementation or a balanced diet [1].

Long-term use of loop diuretics leads to multifaceted electrolyte disturbances, characterized by significant depletion of potassium and chloride along with systemic dehydration. A decrease in blood plasma volume triggers activation of the renin-angiotensin-aldosterone system, which subsequently promotes the secretion of hydrogen ions in the distal tubules of the nephron while simultaneously enhancing bicarbonate reabsorption, resulting in hypochloremic metabolic alkalosis. The clinical presentation of this condition can range from non-specific symptoms, such as generalized weakness and

Table 2
The mechanism of action of diuretics

Diuretic group	Site of action in the nephron	Mechanism of action	Drug example	Clinical significance
Loop diuretics	Thick ascending limb of the loop of Henle	Blocks $\text{Na}^+\text{/K}^+\text{/2Cl}^-$ transporter, reducing sodium and water reabsorption	Furosemide, Torasemide	Main therapy for edema and heart failure
Thiazide diuretics	Distal convoluted tubule	Inhibits $\text{Na}^+\text{/Cl}^-$ reabsorption	Hydrochlorothiazide, Chlorthalidone	Enhance the effect of loop diuretics in resistance
Potassium-sparing diuretics	Distal tubules and collecting tubules	Blocks aldosterone or Na^+ channels	Spironolactone, Eplerenone	Reduce potassium loss and increase diuresis
Carbonic dehydratase inhibitors	Proximal tubule	Reduces bicarbonate reabsorption	Acetazolamide	Additional effect in complex cases of diuretic resistance

cognitive disorientation, to more severe manifestations, including significant cardiac arrhythmias, particularly in geriatric patients or those with impaired renal function. In this context, a critical component of safe pharmacological management involves regular and systematic assessment of electrolytes (K^+ , Cl^- , Na^+) and acid-base balance. When deemed necessary, individualized interventions to correct electrolyte deficiencies and restore fluid balance are appropriate, significantly mitigating the likelihood of cardiovascular complications and ensuring the safe and effective use of diuretic therapy [26, 27].

Regular monitoring of electrolytes and acid-base status is a key safety feature for patients receiving loop diuretics. Monitoring sodium, potassium, magnesium, and creatinine concentrations, especially in the initial stages of therapy or after dose changes, allows for early detection of abnormalities and adjustment of treatment to avoid serious complications. Simultaneous monitoring of fluid volume and renal function reduces the risk of arrhythmias, seizures, and symptomatic hyponatremia. Clinical practice and research results show that regular monitoring of electrolytes and acid-base status allows for early detection of abnormalities, appropriate treatment adjustments, and significantly reduces the risk of complications in patients receiving loop diuretics [1].

Another important consequence of the use of loop diuretics is the effect on calcium metabolism. Blockade of ion transport in the ascending limb of the loop of Henle reduces calcium reabsorption in the kidneys, which leads to increased urinary excretion. In most patients, these changes do not have pronounced clinical manifestations, however, with prolonged treatment or high doses of diuretics, a decrease in calcium levels in the body may be observed. In some cases, this may contribute to the development of muscle weakness or increase the risk of mineral metabolism disorders, especially in elderly patients. Therefore, with prolonged diuretic therapy, it is advisable to take into account possible changes in calcium balance and, if necessary, control its level in the blood [1].

Loop diuretics remove water and sodium from the body through the kidneys, which reduces the volume of circulating blood. This can cause a drop in blood pressure, weakness, dizziness, and difficulty changing body position.

If fluid loss is too great, hypovolemia develops: blood pressure drops, the heart rate increases, and blood supply to the tissues suffers.

Elderly patients and patients with heart failure or chronic diseases are most vulnerable to such changes. Therefore, during treatment with loop diuretics, it is necessary to regularly check blood pressure, assess hydration status, and, if necessary, adjust the dose to prevent excessive fluid loss and complications [16].

In addition, patients, reduced glomerular filtration rate and the presence of comorbidities, such as heart failure or metabolic disorders, increase the risk of developing marked electrolyte imbalances even at moderate doses of loop diuretics. Furthermore, the concurrent use of multiple medications (polypharmacy) may affect renal excretion and electrolyte metabolism, increasing

the likelihood of disturbances in sodium, potassium and magnesium levels. It is precisely because of these factors that advanced age is recognised as one of the key risk factors for the development of diuretic-associated disturbances in electrolyte and acid-base balance [28].

Non-electrolyte side effects of loop diuretics also include gastrointestinal reactions. Some patients may experience symptoms such as nausea, vomiting, abdominal pain or discomfort, diarrhea, or constipation during therapy. These symptoms are usually mild, but they can affect the patient's well-being and reduce the tolerability of treatment. The occurrence of such symptoms is partly due to the pharmacological action of diuretics, which cause significant fluid excretion and changes in circulating blood volume. This, in turn, can affect the blood supply to the digestive system and the functional activity of the intestine. In addition, fluctuations in water and electrolyte balance during intensive diuretic therapy can further contribute to the occurrence of discomfort from the digestive system. In most cases, these reactions do not require discontinuation of treatment, however, in case of severe or prolonged symptoms, it is advisable to assess the patient's condition, review the dosage of the drug and, if necessary, carry out symptomatic correction. This approach allows to maintain the effectiveness of therapy and at the same time improve its tolerability for the patient [29].

One of the non-electrolyte side effects of loop diuretics can be hearing impairment. This is due to the effects of the drugs on the structures of the inner ear responsible for the perception of sound. Clinically, such changes are manifested by ringing in the ears (tinnitus), decreased hearing acuity, or a sensation of muffled sound. In most cases, these disorders are temporary and disappear after a dose reduction or discontinuation of treatment. The risk is increased with high doses, rapid intravenous administration, or concomitant use of other ototoxic drugs, such as aminoglycoside antibiotics. Therefore, it is important to monitor symptoms of hearing impairment during therapy and adjust treatment if necessary [1].

During the use of loop diuretics, some patients may experience certain metabolic changes that are not directly related to electrolyte balance. In particular, an increase in the level of uric acid in the blood has been described, which may contribute to the development of hyperuricemia. Also, clinical observations have noted possible changes in the lipid profile and some disorders of carbohydrate metabolism. Such effects are usually not pronounced in most patients, but may become clinically significant in people with metabolic syndrome, diabetes mellitus, or a predisposition to gout. In this regard, with prolonged use of loop diuretics, it is advisable to periodically assess the indicators of metabolic status in order to adjust therapy in a timely manner if necessary [27].

While taking loop diuretics, a subgroup of patients may experience various changes in the neurological system. These changes often manifest as generalized weakness, increased fatigue, cephalalgia, or a feeling of internal excitement. In some cases, patients may

also report irritability, problems with maintaining concentration, or mild mood swings. Such manifestations include both the significant diuretic effect of pharmacological agents and a decrease in the volume of circulating fluids within the body. In most cases, these symptoms are mild and do not pose a significant threat to health; however, they can affect the patient's general well-being and quality of life throughout the treatment process. Such complaints are especially common among the elderly, since age-related changes in the nervous and cardiovascular systems reduce the body's ability to quickly adapt to fluctuations in water and electrolyte balance.

In light of this, it is important to monitor the appearance of such symptoms during diuretic therapy and assess the patient's general condition. If necessary, the doctor can change the dosage of the drug or re-evaluate the treatment protocol, thereby mitigating the severity of side effects and ensuring a safer administration of loop diuretics [29].

In some patients, taking loop diuretics can cause reactions from the immune system. Most often, this manifests itself on the skin: rash, itching or redness. Usually these symptoms are mild and resolve after stopping the drug or replacing it with another one.

Occasionally, changes in blood tests may be observed, such as a decrease in platelet or neutrophil counts. Although these events are rare, they are clinically important because they may affect the body's ability to fight infections and maintain normal blood clotting.

Therefore, during long-term treatment, attention should be paid to allergic reactions and key blood parameters should be monitored regularly. This helps to identify adverse effects in good time and, if necessary, adjust the treatment [1].

The doctor should also regularly check levels of key electrolytes – potassium, sodium, chloride and magnesium – as well as kidney function by measuring serum creatinine levels, particularly at the start of treatment or following a dose adjustment. Circulating blood volume, blood pressure and signs of dehydration should be monitored regularly. Such monitoring allows early signs of hypovolaemia to be detected and measures to be taken to prevent complications, whilst maintaining the effectiveness of diuretic therapy [29]. In addition to monitoring electrolytes, it is important to be alert to other potential problems associated with loop diuretics. For example, they can affect hearing and cause nausea, vomiting, abdominal pain, diarrhoea or constipation. Metabolic changes sometimes occur: uric acid levels rise, blood lipid levels change or glucose metabolism is disrupted. If changes in the patient's condition are noted, loop diuretics should be selected carefully. Potassium or magnesium can be added to avoid electrolyte deficiencies. The dose can be changed gradually or a different drug can be substituted if it is safer.

The doctor will also look at other medical conditions, such as diabetes, gout, or heart problems, because they can affect treatment and increase the risk of side effects. Particular care is needed in older patients and those with kidney or heart problems.

It is important to regularly check the patient's condition, monitor parameters, and perform blood and kidney tests. This helps to identify problems early, adjust treatment, and reduce the risk of complications. This approach allows for effective and safe treatment [30].

An important element of the safe administration of loop diuretics is adequate patient education and collaborative efforts between healthcare professionals. The patient should formulate the rationale for the treatment, potential adverse effects, and the need to self-monitor body weight, blood pressure, and be vigilant for signs of dehydration, such as thirst, fatigue, or dizziness. This knowledge allows the patient to gain a deeper understanding of their condition and promptly inform the doctor about any changes in their well-being. At the same time, the effectiveness and safety of treatment is significantly influenced by the synergy between the doctor, pharmacist, and nurse. The doctor establishes the treatment strategy and modifies it as needed, the pharmacist monitors the appropriate administration of drugs and assesses potential interactions, while the nurse assesses the patient's condition and adherence to prescribed recommendations. Such collaborative efforts contribute to the early detection of adverse reactions, improve therapeutic monitoring, and help optimize the effectiveness and safety of treatment for the patient [1].

Conclusions.

1. The effectiveness of loop diuretics is largely determined by the achievement of therapeutic concentrations in the kidneys, which depends on the individual characteristics of the patient and the functional state of the heart, kidneys and liver.

2. Diuretic resistance is a common clinical phenomenon and is due to the activity of the distal nephron. Overcoming resistance is achieved not by increasing the dose of the loop diuretic, but by gradually blocking the nephron using a combination with thiazide drugs.

3. Ensuring the safety of therapy requires regular monitoring of electrolyte balance and functional indicators. Special attention should be paid to the risk of hypokalemia and nephrotoxicity/ototoxicity. Minimizing these complications is achieved by avoiding bolus doses and using long-term infusion regimens in high-risk patients.

4. A personalized approach to diuretic prescribing is key, taking into account the pharmacokinetics and pharmacodynamics of the drugs, as well as the patient's general condition. Such a strategy allows maximizing the therapeutic effect while minimizing potential adverse reactions.

Limitations of the study. Our study has several limitations that should be considered when interpreting the presented conclusions. First, these limitations are associated with the review-based nature of the work, as the analysis relied on previously published scientific data without conducting original clinical observations or a meta-analysis. Consequently, the conclusions depend on the quality, completeness, and methodological consistency of the available sources.

An additional factor is the substantial variability in the clinical use of loop diuretics. The efficacy and safety profile of these agents may differ significantly depending

on the underlying disease, severity of cardiovascular or renal failure, concomitant therapy, dosing regimen, and individual patient characteristics. Therefore, the findings of individual studies are not always fully comparable.

Certain challenges also arise in evaluating treatment safety, as different authors apply varying criteria for defining electrolyte disturbances, nephrotoxic effects, or signs of diuretic resistance. Furthermore, a considerable proportion of available clinical data concerns specific patient populations, whereas issues related to the long-term use of loop diuretics, their impact on prognosis, and optimization of treatment regimens in particular subgroups remain insufficiently investigated.

Future research perspectives. Future research on the use of loop diuretics should primarily focus on improving personalized approaches to diuretic therapy according to the patient's clinical condition, characteristics of the underlying disease, renal functional status, age, comorbidities, and risk of electrolyte disturbances. Determining optimal algorithms for the use of loop diuretics in patients with chronic heart failure, chronic kidney disease, nephrotic syndrome, and liver cirrhosis is of particular importance, as the balance between effective decongestion and treatment safety is crucial in these conditions.

An important direction for further investigation remains the study of mechanisms underlying diuretic resistance, including molecular, hemodynamic, and neurohumoral pathways, as well as the development of effective strategies to overcome it. Research into combined diuretic therapy, particularly optimal regimens combining loop diuretics with thiazide or potassium-sparing agents, appears promising and may contribute to enhanced therapeutic efficacy while reducing the risk of adverse effects.

Further studies are also required to investigate the pharmacokinetic and pharmacodynamic characteristics of individual loop diuretics, including bioavailability, duration of action, effects on electrolyte balance, and cardiovascular outcomes. Comparative evaluation of the efficacy and safety profiles of different agents within this drug class in the framework of evidence-based medicine is of particular scientific interest.

Another promising area is the investigation of pharmacogenetic factors influencing individual responses to therapy, which may facilitate the implementation of

personalized medicine in diuretic prescribing practice. Special attention should also be paid to the development of approaches for early monitoring of adverse reactions, dose optimization, and creation of clinical algorithms for the rational use of loop diuretics aimed at improving treatment efficacy and patient prognosis.

Compliance with ethical standards. This article is of a review nature and did not involve clinical or experimental studies involving humans or animals, the use of patients' personal data, or any intervention in the treatment process. Therefore, informed consent and approval by an ethics committee were not required.

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КЛІНІЧНІ ТА ФАРМАКОЛОГІЧНІ ХАРАКТЕРИСТИКИ ПЕТЛЕВИХ ДІУРЕТИКІВ ТА СУЧАСНІ ПІДХОДИ ДО ЇХ РАЦІОНАЛЬНОГО ЗАСТОСУВАННЯ

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Метою роботи є систематизація сучасних даних щодо клініко-фармакологічних властивостей петльових діуретиків та обґрунтування підходів до їх раціонального застосування. **Використано методи** системного аналізу наукової літератури, бібліометричного аналізу та порівняльно-аналітичні підходи. **Результати дослідження** свідчать, що петльові діуретики (фуросемід, буметанід, торасемід) інгібують котранспортер $\text{Na}^+/\text{K}^+/\text{2Cl}^-$ (NKCC2) у товстій висхідній частині петлі Генле, що знижує реабсорбцію електролітів і підсилює діурез. Додатково вони підвищують синтез

простагландинів, покращують ниркову перфузію та клубочкову фільтрацію. Виявлено, що фармакокінетичні відмінності препаратів визначають швидкість початку та тривалість дії. **Отримані результати** можуть бути використані для оптимізації лікування пацієнтів із серцевою недостатністю та іншими захворюваннями, що супроводжуються набряками. **Ключові слова:** петльові діуретики, фармакотерапія, електролітні порушення, НКСС2, діурез, фармакокінетика.

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