Role of loop diuretics in the treatment of acute heart failure

Miejsce diuretyków pętlowych w leczeniu ostrej niewydolności serca

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Abstract

Loop diuretics are used as first-line medications in patients with heart failure as they result in symptomatic improvement related to relieving organ congestion. The recommendations regarding the use of loop diuretics are mostly based on expert opinion, without preference of specific drugs. Thus, the choice of optimal diuretic treatment strategy in acute heart failure requires knowledge about differences in the characteristics of loop diuretics available in Poland, furosemide and torasemide. Non-renal pleiotropic effects of torasemide should be also borne in mind. Clinically significant differences in the pharmacokinetics and biological effects of furosemide and torasemide have been reflected in multiple research studies and meta-analyses published in the recent several years. These studies provided consistent evidence for the good safety profile of torasemide, and its superior efficacy in regard to the improvement of exercise tolerance and reduced readmissions due to heart failure compared to furosemide. The effect of torasemide on mortality reduction in patients with heart failure, seen in some studies, requires further evaluation.

Key words: heart failure, loop diuretics, torasemide, furosemide, chronic kidney disease

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Heart failure

Heart failure is a clinical syndrome related to impaired pump function of the heart, resulting in an inadequate blood flow in relation to the tissue demand [1]. In the pathomechanism of decompensation in patients with heart failure, the major role is played by activation of the renin-angiotensin-aldosterone system, which initially serves as an adaptive mechanism to preserve adequate tissue perfusion and cardiac output. However, increased sympathetic activation, vasoconstriction, and excessive sodium and water retention ensue rapidly, which quickly leads to a significant worsening of heart failure symptoms. In the long-term, it leads to myocardial remodelling and fibrosis, translating to further disease progression [2]. The major factor leading to hospital presentation of patients with heart failure is organ congestion, defined as symptoms of extracellular fluid accumulation [3].

Role of loop diuretics in the management of heart failure

Diuretics are used as first-line medications in patients with heart failure as they result in symptomatic improvement related to relieving organ congestion [4]. The European guidelines on the management of heart failure recommend diuretics to reduce dyspnoea and improve exercise tolerance in patients with symptoms of congestion (class of recommendation I, level of evidence B). In addition, diuretics should be considered to reduce the risk of hospital admission due to heart failure in patients with symptoms of congestion (class of recommendation IIa, level of evidence B) [1]. Although loop diuretics are first-line medications, the recommendations regarding their use are mostly based on expert opinion, without preference of specific drugs [5]. The choice of optimal diuretic treatment strategy in acute heart failure requires

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knowledge about differences in the characteristics of loop diuretics available in Poland.

Mechanism of action of loop diuretics

Loop diuretics available in Poland include furosemide and torasemide. Other drugs from this class, such as azosemide and bumetanide, are not available in Poland. The mechanism of action of loop diuretics involves inhibiting ATP-dependent sodium-potassium-2 chloride cotransporter (NKCC2) located on the luminal surface of the endothelial cells within the thick part of the ascending arm of the loop of Henle. Inhibition of this cotransporter blocks reabsorption of up to 25% of sodium filtered into the primary urine, and this effect is responsible for the most of the natriuretic effect of loop diuretics [6]. In addition, loop diuretics inhibit the same cotransporter at the apical membrane of the macula densa, stimulating renin secretion [7] and blocking the tubuloglomerular feedback [8]—these effects may contribute to preservation of the glomerular filtration rate [4]. Loop diuretics also inhibit the other isoform of this transporter, sodium-potassium-1 chloride cotransporter (NKCC1), which is expressed in the whole body. This effect results in an increased prostaglandin synthesis and venous smooth muscle relaxation, leading to increased venous pooling [9]. The NKCC1 isoform is also expressed in the hearing organ, and this local action of diuretics within the ear likely explains their ototoxicity [10]. Other adverse effects of diuretics include electrolyte disturbances such as hypokalaemia, hypomagnesaemia, hypocalcaemia, hyponatraemia, along with hyperuricaemia and dysglycaemia [5, 11].

Comparison of pharmacokinetics of torasemide and furosemide

Furosemide was introduced to hospital practice in 1966 and it remains the most commonly used loop diuretic. Torasemide was introduced in the United States in 1993 [12].

Following oral administration, furosemide is characterized by limited and variable bioavailability, or the ratio of the absorbed drug to the dose administered orally. The average bioavailability of furosemide is 50% but it ranges from 10% to 100% [13]. Food intake delays furosemide absorption, reducing its peak blood level [4]. As the drug half-life is shorter than its rate of gastrointestinal absorption, it showed an absorption-limited pharmacokinetics [14] which means that the actual half-life following oral administration is longer than the half-life after intravenous administration. In patients with preserved renal function, furosemide administered intravenously is roughly twice more potent per mg compared to oral administration. However, with severe sodium retention in exacerbated chronic heart failure, a higher peak drug level may be required and intravenous

administration may be more effective compared to the oral dose [4]. Although intestinal mucosal oedema and slow blood flow in the duodenum present in heart failure usually do not affect the bioavailability of orally administered drugs, these factors do slow down their absorption, which reduces the peak blood level of the drug and may contribute to resistance to diuretics [15].

In contrast to furosemide, torasemide is characterized by higher and more stable bioavailability following oral administration (> 90%), which is much dependent on concomitant food intake and pH of the gastric contents [16]. Torasemide does not show intestinal absorption-limited pharmacokinetics, which is associated in higher equivalence of oral and intravenous doses [15]. The drug is metabolized in the liver to inactive metabolites, in contrast to furosemide which is mostly excreted by the kidneys [4]. Torasemide has a longer half-life (3–4 h) than furosemide (1.5–2 h). In heart failure, the half-life increases to 6 h for torasemide and 2.7 h for furosemide [13].

Loop diuretics are organic anions circulating in the form of complexes with plasma proteins (> 90%) which limits their distribution volume [4].

Selected pharmacokinetic properties of furosemide and torasemide are shown in Table 1 [16–18].

Comparison of pharmacodynamics of torasemide and furosemide

The onset of action of furosemide and torasemide is within 10 minutes after intravenous administration. The initial observed effect is venous vasodilation [9]. Clinically, it reduces dyspnoea which is often the major complaint in patients with exacerbation of chronic heart failure. Later, these drugs induce diuresis secondary to NKCC2 inhibition in the nephron as described above [13].

Torasemide and furosemide differ in their potency. A double-blind randomized study published in 1986 which compared the diuretic effect of these two drugs showed a relative increase in urine volume by 68% with torasemide compared to furosemide. In addition, a reduction in diuresis at 12 hours after furosemide administration was observed, while this effect was not seen after administration of torasemide [17].

In contrast to furosemide, torasemide shows pleiotropic effects in organs other than the kidneys [16]. Initially, it was observed that torasemide results in lower urinary potassium excretion, an effect similar to that of mineralocorticoid receptor blockade [19]. Later, animal studies confirmed an anti-aldosterone effect of torasemide by blocking aldosterone binding to the mineralocorticoid receptor [20], inhibition of aldosterone secretion [21], and changes in the expression of genes participating in the pathomechanism of myocardial fibrosis [22]. These effects were not demonstrated for furosemide. The anti-aldosterone effect

Table 1. Comparison of selected pharmacokinetic properties of furosemide and torasemide (based on [16–18])

Parameter	Furosemide	Torasemide
Bioavailability following oral administration [%]	10–90 (interindividual variability)	80–90
Effect of food on complete absorption	Yes	No
Relative potency	1 ×	2 ×
Binding with plasma proteins [%]	95	99
Half-life in healthy individuals [h]	1.5–2	3–4
Half-life in chronic kidney disease [h]	2.8	4–5
Half-life in heart failure [h]	2.7	6
Duration of action after intravenous administration [h]	6–8	6–16
Onset of action after intravenous administration [min]	10	8
Peak level after oral administration [h]	1	1
Intravenous to oral dose equivalence ratio	2:1	1:1
Hepatic metabolism (%)	No	80%
Renal excretion	50% conjugates	Mainly in the form of inactive metabolites

Table 2. Comparison of selected pharmacodynamics properties of furosemide and torasemide (based on [16–18])

Parameter	Furosemide	Torasemide
Vasodilating effect preceding the diuretic effect	Yes	Yes
Reduction of kaliuresis	No	Yes
Activation of the renin–angiotensin–aldosterone system	Yes	No or minimal
Sympathetic activation	Yes	No

of torasemide in the comparative study with furosemide [23], which may reduce myocardial fibrosis, also translated to a dose-dependent improvement of clinical heart failure markers, such as natriuretic peptide levels and echocardiographic parameters of left ventricular function. The anti-aldosterone component of the torasemide action may be associated with a reduced risk of hypokalaemia and hypomagnesaemia during intensive combined diuretic therapy [24]. Another advantage is absence of sympathetic activation during torasemide treatment [25]. In addition, torasemide may show benefits in regard to the risk of acute kidney injury. This property was shown in a meta-analysis of randomized studies comparing torasemide to other loop diuretics [26]. A protective effect on the kidney function may be due to an increased secretion of vasodilating prostacyclin, the effect that is more pronounced following torasemide administration compared to furosemide [27]. In addition, furosemide, but not torasemide, stimulates release of thromboxane, a physiological prostacyclin antagonist, in both patients with congestive heart failure and healthy controls [27]. Another possible benefit from the use of torasemide may be a lower risk of ototoxicity. In studies in cats, the dose resulting in a certain level of

hearing impairment in 50% of animals was slightly higher for torasemide compared to furosemide. Hearing impairment tended to improve following the acute phase. In addition, the major metabolite of torasemide did not exert an ototoxic effect even in large doses [28].

Selected pharmacodynamic properties of furosemide and torasemide are shown in Table 2 [16–18].

Renal function and loop diuretics

The common effect of diuretics is a reduction of intravascular volume. A secondary effect is a return of extravascular fluid to restore intravascular volume excreted with urine, known as ‘refilling’ [18]. This effect allows gradual reduction of organ congestion, or fluid accumulation in the extravascular compartment – interstitial tissue and body cavities. Use of high-dose diuretic therapy, resulting in a reduction of intravascular volume, is associated with haemoconcentration which has been identified as a factor leading to transient renal function worsening [29]. The major cause of this problem is likely a disproportion between the diuresis rate and the refilling rate [18], resulting in relative hypovolemia and secondary neural activation accompanied

Figure 1A, B. Comparison of practical aspects of loop diuretic use

by arterial constriction, leading to a risk of peripheral organ ischaemia. One marker of relative hypovolemia and severe neuroactivation in heart failure is urea retention [30]. To counteract these processes, a concept has been advanced that the goal of safe therapy of congestion in heart failure should be to keep the diuresis rate during diuretic drug therapy at the level not exceeding the refilling rate [1, 31]. By extrapolating the experience from renal replacement therapy to diuretic treatment, it may be supposed that exceeding the refilling rate is more likely when ultrafiltration is too large over a short time, while the effectiveness of refilling should improve when ultrafiltration is extended over time [32]. Hence, prolonging the duration of a diuretic effect by the use of a long-acting diuretic, torsemide, administered in dosing intervals consistent with its duration of action, should be more effective in this regard [18]. Figure 1 shows practical aspects of furosemide and torsemide use, including episodic occurrence of the effects of profound diuresis following furosemide administration, which may contribute to symptomatic hypotension in the treated patients, and possible reduction in the urine output following cessation of the diuretic action, which may lead to clinically observed recurrent symptoms of congestion, for example in the pulmonary circulation.

When planning the management in a patient with heart failure, due attention should be paid to the phenomenon of diuretic resistance, which may occur in as many as 25–30% of patients with this clinical syndrome. The occurrence of the diuretic resistance phenomenon may be expected in patients with hypotension, chronic kidney disease, and atherosclerosis. The multiple underlying factors include changes in drug pharmacokinetics, hormonal dysregulation, and the cardiorenal syndrome. The management of patients with diuretic resistance includes sequential nephron blockade using diuretics from two different classes,

renal replacement therapy by ultrafiltration or peritoneal dialysis, and aspiration of peritoneal fluid in patients with increased intraabdominal pressure [33]. However, the most commonly used approach is to increase the doses of diuretics drugs to promote a negative fluid and sodium balance. Torsemide, which is characterized by a nearly unchanged half-life in the settings of impaired renal function [16], provides an effective dose-dependent increase in diuresis and natriuresis when used in high doses, even in patients with advanced chronic kidney disease. Two multi-centre clinical trials which compared high furosemide and torsemide doses in patients with end-stage renal disease undergoing haemodialysis showed a large increase in urine output and ion excretion in patients treated with 100 mg or 200 mg torsemide once daily orally. The oral daily torsemide dose of 200 mg resulted in a similar natriuretic effect compared to the oral furosemide dose of 500 mg, with more potent blood pressure-lowering effect of torsemide. Both torsemide and furosemide in these doses had no negative effect on the neurological status of patients treated with haemodialysis [34].

Torsemide 200 mg preparation is available in Poland for the treatment of patients with severe chronic kidney disease (creatinine clearance < 20 mL/min and/or serum creatinine level > 6 mg/dL). The indication for its use is the intent to preserve diuresis, and the presence of oedema, transudate, and high blood pressure in patients with severe renal failure, including dialyzed patients, if the residual diuresis exceeds 200 mL/day.

Clinical studies comparing torsemide and furosemide

The extremely clinically important differences in the pharmacokinetic properties and biological effects of furosemide

and torasemide have been reflected in many research studies published in the last several years that evaluated the efficacy and safety of torasemide. The comparator is most of these studies was furosemide, a diuretic commonly used for many years.

In an open German study [35] in 1650 patients to compare the clinical efficacy of torasemide and furosemide, it was shown that torasemide resulted in the greatest improvement in exercise tolerance in patients with initially severe symptoms and/or those diuretic-naïve. Patients previously treated with a diuretic benefited from a switch to torasemide. No adverse effects on potassium, uric acid, and glucose levels were observed in the torasemide group. In that study, 95% of physicians and 93% of patients positively rated their experiences with torasemide treatment.

In a one-year open randomized study [36] in 234 patients that compared furosemide and torasemide, patients treated with torasemide had a lower rate of readmissions due to heart failure (17% vs. 32% in the furosemide group) and cardiovascular hospitalizations (44% vs. 59% in the furosemide group). In addition, patients treated with torasemide spent fewer days in hospital due to heart failure, and reported better improvement in terms of dyspnoea and fatigue. Reduction in hospitalization due to heart failure observed during torasemide therapy translates to a lower cost of treating patients with chronic heart failure despite a higher cost of drug acquisition [37, 38].

Nine-month open randomized study [39] in 237 patients with decompensated heart failure evaluated the quality of life of patients treated with torasemide or furosemide. Compared to furosemide, torasemide resulted in a significant symptom improvement [by at least one New York Heart Association (NYHA) class] and was associated with better treatment tolerance, lower number of micturiations at 3, 6, and 12 hours after dosing, and lower severity of urgency. Despite a milder, and thus more comfortable diuretic action profile, torasemide resulted in twice higher reduction in body weight that served as a surrogate measure of fluid overload.

The purpose of open, nonrandomized TORIC study [40] was to compare 1377 patients with NYHA class II–III heart failure who received oral treatment with torasemide 10 mg/day, furosemide 40 mg/day or other diuretics orally for 12 months in addition to standard heart failure therapy. Treatment safety and tolerance, mortality, NYHA functional class, and blood potassium level were evaluated every 3 months. Overall mortality was 51.5% lower ($p < 0.05$), and cardiovascular mortality 59.7% lower ($p < 0.05$) in the torasemide group. In addition, clinical improvement was noted more frequently in the torasemide group ($p < 0.00017$). Treatment with torasemide was associated with less frequent adverse effects – potassium level below 3.5 mmol/L was noted in 12.9% of patients treated with torasemide, compared to 17.9% of patients treated with furosemide

($p = 0.013$). In addition, potassium supplementation was required in only 3% of patients treated with torasemide, compared to 30% of patients treated with furosemide.

In a multicentre double-blind randomized study [41], 6-week therapy with torasemide 10 mg/day, torasemide 20 mg/day and furosemide 40 mg/day was compared in 70 patients with chronic heart failure who were previously treated with furosemide 40 mg/day for at least 2 weeks. A significant reduction in body weight was noted in all three groups but this effect was significantly greater in the torasemide 20 mg group at 4 and 6 weeks compared to furosemide and in the torasemide 10 mg group at 4 weeks compared to furosemide. At 6 weeks, the torasemide 20 mg group also showed significantly less severe oedema compared to furosemide ($p = 0.001$).

Initial results of the Polish multicentre randomized TORNADO study were also reported [42]. This study was conducted in 40 patients with NYHA functional class II–IV previously treated with furosemide who were assigned to the treatment with equipotent torasemide dose or continuation of furosemide at the same dose. During the follow-up, 7 patients were hospitalized due to exacerbation of heart failure, including 3 patients in the torasemide group and 4 patients in the furosemide group. The combined endpoint evaluated at 3 months of treatment was defined as improved NYHA class, improvement by at least 50 m in the 6-minute walking test, and reduction of objectively evaluated congestion. This endpoint was reached by 94% of patients in the torasemide group and 58% of patients in the furosemide group ($p = 0.03$), indicating an advantage of torasemide over furosemide in reducing congestion and heart failure symptoms as early as after 3 months of therapy.

The ongoing multicentre randomized TRANSFORM-HF study [43] should also be noted. This study will be conducted in the so far largest group of 6,000 patients hospitalized due to heart failure who will be randomized to oral furosemide or torasemide before the hospital discharge.

Meta-analyses and systematic reviews comparing torasemide and furosemide

Meta-analyses of small randomized studies [44, 45] showed that compared to placebo, loop and thiazide diuretics increase exercise tolerance, reduce hospitalizations due to exacerbated heart failure, and even reduce the mortality risk by more than 70%. Due to a small number of deaths in the study groups, however, the results of these meta-analyses should be interpreted with caution.

A meta-analysis of randomized studies [46] comparing the efficacy of torasemide and furosemide in 471 patients with systolic heart failure showed that torasemide reduced hospitalizations due to heart failure and cardiovascular hospitalizations. In addition, a 14% reduction in

the total mortality in the torasemide group was noted but this effect was statistically not significant.

In a later meta-analysis of randomized studies [26] comparing the efficacy of torasemide with other loop diuretics in 2,647 patients, no differences in the overall and cardiovascular mortality were noted but fewer hospitalizations occurred in the torasemide group.

However, a dose-dependent association between loop diuretic use and the mortality risk was also noted in patients with advanced heart failure of ischaemic aetiology [47]. In contrast to these results, it was showed that a higher loop diuretic dose prescribed at discharge after a hospitalization due to exacerbated chronic heart failure with reduced ejection fraction reduced the risk of readmission within 30 days [48]. It is believed that the need to use a higher loop diuretic dose indicates a higher severity of heart failure but is not the cause for worse outcomes in these patients [49].

In the meta-analysis [50] of 19 studies (9 randomized controlled and 10 observational) published in 1996–2019 which included 19,280 patients with heart failure treated with torasemide and furosemide, with the mean follow-up of 15 months, a lower risk of hospitalization due to heart failure was shown in the torasemide group compared to furosemide (10.6% torasemide, 18.4% furosemide; odds ratio [OR] 0.72, 95% confidence interval [CI] 0.51–1.03, $p = 0.07$). Torasemide use was associated with a significantly higher chance of improvement from NYHA class III–IV to class I–II (72.5% torasemide, 58% furosemide; OR 2.32, 95% CI: 1.32–4.1, $p = 0.004$) and a lower risk of death due to cardiovascular causes (1.5% torasemide, 4.4% furosemide; OR 0.37, 95% CI: 0.20–0.66, $p < 0.001$) compared

to furosemide. However, no reduction in the total mortality or adverse effects was shown.

In another meta-analysis [51] of 54 randomized controlled studies in 10,740 patients with heart failure, various diuretic treatment was compared. This study showed that compared to furosemide, torasemide treatment over 1.5–5.6 months of follow-up reduced oedema (relative risk 1.54, 95% CI: 1.01–2.35) and resulted in a greater reduction of blood natriuretic peptide levels. This study showed no differences between various diuretics in the rates of adverse effects involving various organs, and no differences in readmissions and mortality.

Summary

Heart failure is a major challenge for modern cardiology, and also an important problem for healthcare management systems due to its large economic and social burden [52]. The most important limitation for widespread use of torasemide remains the lack of evidence from appropriately large, prospective, randomized, placebo-controlled studies. However, as performing such studies in patients with full-blown symptomatic acute exacerbated heart failure may not be possible, the optimal drug therapy must be guided by the available clinical study results and these suggest that in patients with acute exacerbated heart failure, torasemide is an appropriate alternative for commonly used furosemide. A wider use of torasemide, which is characterized by better pharmacological properties, a longer and more potent effect, and a documented reduction of the readmission rate, seems more appropriate from the clinical and economic perspective.

Streszczenie

Leki moczopędne podaje się w farmakoterapii pierwszego rzutu u pacjentów z niewydolnością serca, ponieważ powodują poprawę objawową w zakresie zastojów narządowego. Podstawą zaleceń dotyczących stosowania diuretyków pętlowych są głównie opinie ekspertów, bez wskazania konkretnego leku. Wybór optymalnej strategii leczenia moczopędnego w ostrej niewydolności serca wymaga zatem od zespołu lekarskiego wiedzy na temat różnic we właściwościach i specyfice działania dostępnych na polskim rynku diuretyków pętlowych – furosemidu i torasemidu. Należy również pamiętać o plejotropowym działaniu torasemidu wykraczającym poza lokalizację nerkową. Istotne klinicznie różnice pod względem właściwości farmakokinetycznych i efektów biologicznych furosemidu i torasemidu znalazły odzwierciedlenie w wielu badaniach naukowych oraz metaanalizach opublikowanych w ostatnich kilkunastu latach. W badaniach tych konsekwentnie potwierdzano dobry profil bezpieczeństwa torasemidu, jak również wykazano większą skuteczność torasemidu w zakresie poprawy wydolności fizycznej u pacjentów oraz zmniejszenie częstości ponownych hospitalizacji z powodu niewydolności serca w porównaniu z furosemidem. Tematem dalszych dociekań pozostaje potwierdzenie w niektórych badaniach wpływ torasemidu na zmniejszenie śmiertelności u pacjentów z niewydolnością serca.

Słowa kluczowe: niewydolność serca, diuretyki pętlowe, torasemid, furosemid, przewlekła choroba nerek

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