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COMPARISON OF CLINICAL EFFECTIVENESS OF LOOP DIURETICS IN COMPLEX THERAPY OF CHRONIC HEART FAILURE

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Abstract.

The article discusses the features of the mechanism of action of diuretics. A comparative analysis of diuretics is carried out depending on the point of action, as well as a comparison of the pharmacological properties of drugs of the same class (loop diuretics - furosemide and torsemide). The authors observed patients with chronic heart failure (CHF).

Purpose of the study: to evaluate the effectiveness and safety of torasemide (Lotonel, Vertex) in patients with CHF.

Material and methods: The study involved 58 patients with CHF who were randomized into 2 groups: 20 patients received torsemide (Lotonel, Vertex) in addition to the main therapy for 3 months, and 38 patients received furosemide. Patients included in the study had clinical signs of stage II-III CHF. The examination of patients included determination of the NYHA FC of CHF, the severity of the clinical condition using the Clinical Status Assessment Scale (CSAS), registration of a 12-lead ECG, echocardiography, blood sampling to determine indicators of electrolyte metabolism and creatinine, as well as a 6-minute walk test.

Results and conclusion: Initially and after 3 months. During therapy, all patients were assessed for their clinical condition, hemodynamic status, quality of life and functional state of the left ventricle (LV), and the levels of electrolyte metabolism and creatinine were determined. The effect of both diuretics on body weight, edema, and shortness of breath was comparable. In both groups, according to EchoCG data after 3 months. There was a decrease in end-diastolic volume (EDV), as well as a significant increase in LVEF. In the torasemide group, there was a significant increase in the 6-minute walk distance; torasemide had a lesser effect on potassium excretion. The safety and effectiveness of the use of torasemide and furosemide to improve the clinical condition and quality of life of patients with moderate compensated CHF were confirmed. However, the clinical and hemodynamic characteristics of torasemide were superior to those of furosemide.

Key words: Patients with CHF, chronic heart failure, diuretics, torasemide, furosemide.

SURUNKALI YURAK YETISHMOVCHILIGINI KOMPLEKS DAVOLASHDA DIURETIKLARNING KLINIK SAMARADORLIGINI QIYOSLASH

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Annotatsiya

Maqolada diuretiklarning tasir qilish mexanizmining xususiyatlari ko‘rib chiqiladi. Diuretiklarning qiyosiy tahlili tasir nuqtasiga qarab, shuningdek bir xil sinfdagi dorilarning farmakologik xususiyatlarini taqqoslash (petleviy diuretiklar - furosemid va torsemid) o‘tkazildi. Muallif surunkali yurak etishmovchiligi (SYuE) bo‘lgan bemorlarni kuzatdi.

Tadqiqot maqsadi: SYuE bilan og‘rigan bemorlarda torasemidning (Lotonel, Vertex) samaradorligi va xavfsizligini baholash.

Material va usullar: Tadqiqotda SYuE bilan kasallangan tasodifiy 2 guruxda 58 bemor ishtirok etdi: 20 bemor 3 oy davomida asosiy terapiyaga qo‘shimcha ravishda torsemid oldi, 38 bemor furosemid oldi. Tadqiqotga kiritilgan bemorlarda SYuE II-III bosqichining klinik belgilari mavjud edi. Bemorlarni tekshirish CYuE ning NYHA VS ni aniqlash, Klinik holatni baholash shkalasi (KXBSh) bo‘yicha klinik holatning og‘irligini, 12 tarmoqli EKGni ro‘yxatdan o‘tkazish, ExoKG, elektrolitlar almashinuvi va kreatinin ko‘rsatkichlarini aniqlash. Qon namunalarini olish va 6 daqiqalik yurish testi o‘tkazishdan iborat.

Natijalar va xulosa: Dastlab va 3 oydan keyin. Terapiya davomida barcha bemorlarda klinik holat, gemodinamik holat, hayot sifati va chap qorincha (ChQ) funktsional holati baholandi, elektrolitlar almashinuvi va kreatinin darajasi aniqlandi. Ikkala diuretikning tana vazniga, shish va nafas qisilishiga tasiri o‘xshash edi. Ikkala guruhda ham 3 oydan keyin ExoKG malumotlariga ko‘ra. Diastolik end-diastolik hajmda (EDV) pasayish, shuningdek, FV ChQ da sezilarli o‘sish kuzatildi. Torsemid guruhida 6 daqiqalik yurish masofasida sezilarli o‘sish kuzatildi; Torsemid kaliyning chiqarilishiga kamroq tasir ko‘rsatdi. O‘rtacha kompensatsiyalangan SYuE bo‘lgan bemorlarning klinik holati va hayot sifatini yaxshilash uchun torasemid va furosemiddan foydalanish xavfsizligi va samaradorligi tasdiqlangan. Biroq, torasemidning klinik va gemodinamik xususiyatlari furosemid-nikidan ustun.

Kalit so‘zlar: ChF bilan og‘rigan bemorlar, surunkali yurak etishmovchiligi, diuretiklar, torasemid, furosemid.

СРАВНЕНИЕ КЛИНИЧЕСКОЙ ЭФФЕКТИВНОСТИ ПЕТЛЕВЫХ ДИУРЕТИКОВ В КОМПЛЕКСНОЙ ТЕРАПИИ ХРОНИЧЕСКОЙ СЕРДЕЧНОЙ НЕДОСТАТОЧНОСТИ

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В статье рассматриваются особенности механизма действия диуретиков. Проведен сравнительный анализ диуретиков в зависимости от точки действия, а также сравнение фармакологических свойств препаратов одного класса (петлевые диуретики - фуросемид и торасемид). Авторы наблюдали больных хронической сердечной недостаточностью (ХСН).

Цель исследования: оценить эффективность и безопасность торасемида (Лотонел, Вертекс) у больных ХСН.

Материал и методы: В исследовании приняли участие 58 больных ХСН, которые были рандомизированы на 2 группы: 20 больных получали торасемид (Лотонел, Вертекс) в дополнение к основной терапии в течение 3 мес, 38 больных получали фуросемид. Patsienты, включенные в исследование, имели клинические признаки ХСН II-III стадии. Обследование больных включало определение ФК ХСН по NYHA, тяжести клинического состояния по шкале оценки клинического статуса (CSAS), регистратsiю ЭКГ в 12 отведениях, эхокардиографию, забор крови для определения показателей электролитного обмена и креатинина, а также тест 6-минутной ходьбы.

Результаты и заключение: Первоначально и через 3 месяца. В ходе терапии у всех patsientов оценивали клиническое состояние, гемодинамический статус, качество жизни и функциональное состояние левого желудочка (ЛЖ), определяли уровень электролитного обмена и креатинина. Влияние обоих диуретиков на массу тела, отеки и одышку было сопоставимым. В обеих группах по данным ЭхоКГ через 3 мес. Отмечалось снижение конечно-диастолического объема (КДО), а также значительное увеличение ФВЛЖ. В группе торасемида наблюдалось значительное увеличение дистанции 6-минутной ходьбы; торасемид оказывал меньшее влияние на экскрецию калия. Подтверждена безопасность и эффективность применения торасемида и фуросемида для улучшения клинического состояния и качества жизни patsientов с умеренной компенсированной ХСН. Однако клинические и гемодинамические характеристики торасемида превосходили показатели фуросемида.

Ключевые слова: Больные ХСН, хронической сердечной недостаточностью, диуретики, торасемид, фуросемид.

Introduction. In recent years, there has been an increase in the number of patients with CHF all over the world. This is associated with increased life expectancy and disease comorbidity. By 2050, the prevalence of CHF is expected to increase by 60% compared to 2010 [1, 2].

The main causes of CHF development are arterial hypertension (AH) (88% of cases), coronary heart disease (CHD) (59% of cases). The combination of these diseases occurs in every second patient with CHF [3]. Moreover, among all cardiac patients, the main reason for hospitalization in 16.8% of cases is decompensation of CHF [4]. Particularly important is the fact that mortality among patients with stage III-IV CHF. very high - 50% of patients die within 1 year [2].

Clinically, decompensation of CHF is manifested by increased shortness of breath, congestion in the lungs and edema of the lower extremities. The main directions of therapy are the normalization and regulation of the volume or composition of body fluids, which is achieved by prescribing diuretics [5].

The choice of diuretics is very important, since irrational prescription of drugs in this group is one of the causes of decompensation of CHF [6].

Diuretics are a diverse group of drugs that increase the volume of urine produced. Diuretics also increase the excretion of sodium and water, suppressing the mechanism of sodium reabsorption in different parts of the renal tubules. In addition, these drugs affect the excretion of potassium, magnesium, chlorine, phosphates and bicarbonates, which, with long-term use, results in various side effects. Diuretics differ in their mechanism and strength of action, ability to influence acid-base balance, speed of onset and duration of action. They are used in complex therapy of hypertension, because they have a hypotensive effect and enhance the effectiveness of other antihypertensive drugs. In the treatment of CHF, the property of diuretics to reduce pulmonary edema and venous pulmonary hypertension is used [7–9].

According to the mechanism of action, drugs are divided into 6 classes (Table 1) [7, 10–12].

CLASSIFICATION OF DIURETICS			
Name	Scene	Force of action	Mechanism of action
Loopback	Ascending loop of henle	Powerful	Sodium potassium and chlorine transport inhibitors
Thiazide	Distal tubule	Moderate	Sodium and chlorine transport inhibitors
Carbonic anhydrase inhibitors	Proximal tubule	Weak	Carbonic anhydrase inhibitors
Potassium-sparing diuretics	Terminal part of the proximal Canadian and collecting ducts	Weak	Renal epithelial sodium channel blockers
Mineralocorticoid receptor antagonists	Terminal part of the proximal Canadian and collecting ducts	Weak	Mineralocorticoid receptor blockers
Osmotic diuretics	Proximal tubule	Strong	Osmotic diuretics

Thiazide and thiazide-like diuretics (TDs) are very common due to their effectiveness. With CHF I stage. their intake does not require too strict restriction of salt intake [13, 14]. This group consists of hydrochlorothiazide and non-thiazide sulfonamides (chlorthalidone, indapamide, clopamide). The main site of action of TD is the initial part of the distal convoluted tubule. The proximal region is an additional site of action.

The main differences between TD and loop diuretics are a decrease in calcium excretion and an increase in sodium concentration in the distal nephron, which leads to increased exchange of sodium for potassium with increased excretion of the latter [15].

TDs do not alter renal blood flow and reduce glomerular filtration rate (GFR) under certain conditions. A representative of this group, indapamide, increases GFR and has a hypotensive effect in hypertensive patients with normal and reduced renal function. The ability of TD to reduce vascular resistance and cause a hypotensive effect is associated with the main saluretic effect of these drugs.

Low doses of TD are used in the treatment of hypertension. Higher doses are used in the treatment of edema syndrome and CHF; in this case, noticeable shifts in plasma concentrations of potassium, uric acid, glucose and lipids are observed, which creates contraindications [16].

Carbonic anhydrase inhibitors (CA). Currently, drugs in this group have limited use as diuretics. A representative of IC is acetazolamide, which is a sulfonamide derivative. Acetazolamide inhibits the enzyme carbonic anhydrase, which catalyzes the formation of hydrogen ions in tubular epithelial cells. Hydrogen ions in the lumen of the tubule are exchanged for sodium ions, which enter the epithelial cell. During this exchange involving carbonic anhydrase decreases sodium reabsorption and increases the excretion of bicarbonates, which is accompanied by the development of metabolic acidosis. Acetazolamide blocks carbonic anhydrase in the proximal tubule region. In the treatment of CHF, it is used as an additional agent during long-term treatment with strong diuretics to normalize urine pH and restore sensitivity to loop diuretics when resistance occurs. The most common indications are edema syndrome in combination with alkalosis, glaucoma, intracranial hypertension [12, 14,].

Potassium-sparing diuretics (KDs). According to the mechanism of action, KDs are divided into 2 groups: agents that block sodium channels of renal epithelial cells and mineralocorticoid receptor antagonists. The most

commonly used CDs are veroshpiron, spironolactone, and triampur. These drugs have one serious side effect - the risk of hyperkalemia, especially in patients with diabetes mellitus, renal failure, or when combined with ACE inhibitors or potassium supplements[11].

Sodium channel blockers. KDs block sodium channels of the epithelium in the distal tubules and collecting ducts. However, the diuretic effect of drugs in this group is weakly expressed, since the reabsorption capacity of the collecting ducts is limited and amounts to approximately 2% of the total filtered volume of salts.

Mineralocorticoid receptor antagonists (MCRA). Spironolactone enhances the effect of diuretics of other groups. Indications for use, in addition to CHF, are edema in liver cirrhosis, primary hyperaldosteronism (Conn's disease). Due to the possibility of hyperkalemia, strict laboratory monitoring is necessary. A better alternative to spironolactone is eplerenone, a competitive selective AMCR in the distal nephron.

AMKR exhibit maximum effect in combination with other neurohormonal modulators (ACE inhibitors or sartans, beta blockers). These drugs are used for triple neurohormonal blockade in the treatment of CHF. The goal of therapy is to reduce the risk of cardiovascular complications and mortality in patients with left ventricular dysfunction (EF<40%) and clinical manifestations of CHF after a recent myocardial infarction. In case of severe decompensation and worsening of CHF, CDs are used in high doses in combination with loop diuretics [10].

The level of potassium in plasma must be determined before the start of therapy, then after 1 week, 1 month; also when changing the dose and periodically during treatment (especially in the elderly, with renal failure, diabetes mellitus). With potassium values in plasma 5.5–5.9 mmol/l requires a dose reduction; more than 6 mmol/l – discontinue the drug [15].

Osmotic diuretics (OD). Representatives of this class are mannitol, urea, glycerin, isosorbide. These diuretics act in the proximal tubule. Being osmotically active substances, they increase the osmolarity of plasma and tubular fluid. The drugs are not reabsorbed, as a result they prevent the movement of water into the interstitium, the concentration of sodium in the tubules is significantly reduced, which leads to the cessation of its reabsorption. At the level of the loop of Henle, ODs also act, although to a lesser extent than loop ones. As a result of taking OD, the volume of extracellular fluid increases, blood viscosity decreases, renal blood flow

increases, and oncotic pressure in the glomeruli decreases. Indications for the prescription of diuretics of this group are attacks of glaucoma, cerebral edema, and prevention of a decrease in GFR during surgical interventions [11, 14, 16].

Loop diuretics (LDs). They have the most powerful diuretic effect, and their use is recommended for patients with severe manifestations of CHF [5]. PDs cause dilatation of renal and peripheral vessels [14].

One of the widely used drugs in this class is furosemide. However, its constant use causes a decrease in the quality of life in patients, which is expressed in the imperative urge to urinate in the first 2 hours after taking the drug, and severe hypotension is recorded. In general, all these effects lead to a decrease in compliance [8]. It is known that diuretic therapy (most often furosemide) using small doses of the drug and a “weekend” regimen (taking the drug every other day or on weekends) is unjustified and provokes the development of decompensation of heart failure [2, 6]. The unique properties of torasemide, including its favorable pharmacokinetic profile for outpatient administration (longer half-life and duration of action, as well as higher bioavailability compared with those of furosemide), may overcome these difficulties and concerns of maintenance diuretic therapy. In recent ears, the PD torasemide has been successfully used .

Torasemide, unlike furosemide, also blocks the effects of aldosterone, i.e., it increases renal excretion of potassium to a lesser extent. This reduces the risk of hypokalemia, one of the main side effects.

The pharmacokinetic properties of torasemide differ from those of furosemide; the differences are presented in Table 2 .

COMPARATIVE CHARACTERISTICS OF FUROSEMIDE AND TORASEMIDE

Characteristics	Furosemide	Torasemide
Bioaailability (%)	50	80 - 100
Reduced bioavailability with food	Yes	No
Metabolism	50 - 50	Kidneys/liver 20 - 80
Onset of action after oral admin-istration min	30 - 60	30 - 60
T1/2(h) with CHF	2,7	3- 6
T1/2(h) with renal dysfunction	2,8	4 - 5
T1/2(h) with liver dysfunction	2,5	8

The largest study of torsemide is the open randomized trial TORIC (TORsemide in Congestive heart failure), which compared fixed doses of 40

mg/day furosemide and 10 mg/day torsemide in more than 2 thousand patients with CHF. A significantly lower ($p<0.05$) overall and cardiovascular mortality was proven in the group of patients taking torasemide. Treatment with torasemide was superior in terms of functional class reduction and was less likely to cause hypokalemia[12].

Standard doses of torasemide for the treatment of CHF are 10–20 mg/day. For cirrhosis of the liver with ascites, torasemide is taken together with aldosterone antagonists on a low-salt diet.

The mechanism of action of torasemide is the reversible binding of torasemide to the sodium/chlorine/potassium ion cotransporter located in the ascending segment of the loop of Henle, as a result of which the reabsorption of sodium and water is reduced or completely inhibited, and the osmotic pressure of the intracellular fluid decreases. Torsemide blocks myocardial aldosterone receptors, reduces the progression of fibrosis and improves myocardial diastolic function.

The antialdosterone effect of torasemide causes less hypokalemia than that of furosemide, while torasemide is more active and its action is longer .

The diuretic effect of torasemide lasts up to 18 hours. The absence of frequent urination in the first hours after taking the drug significantly improves the patient's quality of life and increases compliance. The purpose of this study was to compare the safety of long-term therapy and the effect of torasemide (Lotonel, Vertex, Russia) and furosemide on the course of the disease and quality of life, LV function and electrolyte levels in patients with compensated CHF who do not require intravenous PD.

Material and methods. We observed 58 patients over the age of 40 ears with clinical signs of stage II–III CHF. The CHF therapy received at the start of the study was stable over the past 4 months. The study did not include patients with clinical signs of obvious fluid retention in the body requiring intravenous administration of PD (edema of the lower extremities, hepatomegaly, swelling of the jugular veins, moist rales in the lungs). Non-inclusion criteria also included: clinical signs of hypovolemia, hypokalemia, hemodynamically significant lesions of the heart valves; pulmonary heart; ACS in less than 3 months. before the start of the study; inflammatory diseases, serum creatinine >30 μmol/l.

All patients underwent a clinical examination with determination of the FC of CHF according to NYHA, the severity of the clinical condition using the Clinical Status Assessment Scale (CSAS). An ECG was recorded in 12 leads, an

EchoCG was performed according to standard methods, and blood was taken to determine indicators of electrolyte metabolism and creatinine. A 6-minute walk test was conducted. All patients were randomly divided into 2 comparable groups: 1st received torasemide 10–20 mg/day (n=20), 2nd received furosemide 10–60 mg/day (n=18). The starting dose of torasemide was selected depending on the diuretic therapy used at the time of initiation of therapy. All patients received standard therapy for CHF (ACE inhibitors or sartans, β-blockers, aldosterone antagonists, cardiac glycosides as indicated). Both drugs were prescribed in combination with 50–100 mg/day of veroshpiron. At the same time, at visits 1 (after 7 days) and 2 (after 1 month), a clinical examination and blood sampling were performed, and at the final visit 3 (3 months), in addition, echocardiography was performed at rest. Therapy with the study drugs was not accompanied by clinically significant fluctuations in blood pressure and heart rate. None of the patients had adverse reactions that required exclusion from the study.

Results. Positive dynamics in the clinical condition of patients and the severity of CHF were noted in both groups. The effects of both diuretics on body weight, edema, and dyspnea were comparable. A more rapid reduction in symptoms of shortness of breath, palpitations, disappearance of peripheral edema or pastosity in combination with effective blood pressure control was observed among patients in the torasemide group (differences not significant). Daily diuresis was 2.24 and 2.46 l/day, respectively, in the torasemide and furosemide groups (the differences are not significant).

During the study, in both groups there was a significant decrease in the average NYHA FC by 11% in the torasemide group and by 6% in the furosemide group ($p < 0.05$).

According to echocardiography after 3 months. in both groups there was an improvement in the functional state of the left ventricle in the form of a decrease in EDV. In group 1, there was a decrease in EDV from 170.1 to 163.4 ml, in group 2 – from 168.5 to 164.3 ml ($p<0.05$), as well as a significant improvement in systolic function (increased EF LV from 46.7% to 50.2% in the torsemide group and from 46.2% to 48.7% in the furosemide group).

In the torasemide group there was a significant increase in the 6-minute walk distance - from 280 to 350 (+70) m, in the furosemide group - from 270 to 310 (+40) m.

However, torasemide had a lesser effect on potassium excretion. During the study, an insignificant decrease in plasma potassium levels was observed

in the torasemide and furosemide groups. The average creatinine level in both groups also remained virtually unchanged.

During diuretic therapy, the appearance of extrasystole (supraventricular and ventricular) was noted according to ECG data. In the torasemide group, extrasystole occurred in 2 (5%) patients, in the furosemide group - in 5 (17%) patients.

Conclusion. Thus, furosemide and torasemide (Lotonel) have a strong natriuretic and, accordingly, diuretic effect. However, the use of torasemide (Lotonel) is the most reasonable choice for long-term treatment of heart failure. The drug has a pronounced diuretic effect, has high bioavailability, a longer duration of action, and an optimal cost-effectiveness ratio. There was a significant decrease in the severity of shortness of breath, an increase in exercise tolerance and an improvement in the quality of life of patients with CHF.

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