THE ROLE OF CALCIUM CHANNEL BLOCKERS IN THE TREATMENT OF ARTERIAL HYPERTENSION AND THE MECHANISM OF ACTION

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РОЛЬ И МЕХАНИЗМ ДЕЙСТВИЯ БЛОКАТОРОВ КАЛЬЦИЕВЫХ КАНАЛОВ В ЛЕЧЕНИИ АРТЕРИАЛЬНОЙ ГИПЕРТЕНЗИИ

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ARTERIAL GIPERTONIYANI KASALLIGINI DAVOLASHDA KALSIY KANAL BLOKATORLARINING O'RNI VA TA'SIR MEHANIZMI

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Summary

At the end of the 20th and the beginning of the 21st century, the global community faced a worldwide issue that is not only medical but also has significant socio-economic implications — the pandemic of chronic diseases. Chronic conditions such as diabetes, heart, lung, and kidney diseases, as well as their various combinations, are now observed in nearly every individual. High-tech intensive and replacement therapies can save lives, but they do not always ensure the preservation of life quality, work capacity, and social activity. Moreover, simple and affordable preventive measures are often underutilized, diseases are diagnosed late, and patients frequently lack motivation and commitment to a healthy lifestyle.

Early clinical and laboratory signs of kidney damage are often vague and go unnoticed by physicians, particularly in elderly patients. These initial symptoms are often perceived as part of the "age norm."

Among chronic non-communicable diseases, chronic kidney disease (CKD) occupies a special place due to its high prevalence, significant reduction in quality of life, and high mortality rates. At its terminal stage, CKD necessitates expensive treatments such as dialysis or kidney transplantation. However, none of the existing kidney replacement therapies are flawless: they fail to fully restore kidney function and carry the risk of complications.

Keywords: *Chronic kidney disease, glomerulosclerosis, calcium channel blockers, remodeling, dihydropyridine, lercanidipine*.

Резюме

В конце XX и начале XXI века мировое сообщество столкнулось с глобальной проблемой, имеющей не только медицинское, но и значительное социально-экономическое значение — пандемией хронических заболеваний. Хронические состояния, такие как сахарный диабет, сердечные, легочные и почечные заболевания, а также их различные сочетания, наблюдаются практически у каждого человека. Высокотехнологичные интенсивные и заместительные методы терапии могут спасти жизнь, но далеко не всегда обеспечивают сохранение ее качества, трудоспособности и социальной активности. Кроме того, простые и доступные меры профилактики часто недостаточно используются, болезни выявляются поздно, а у пациентов зачастую отсутствует мотивация и приверженность здоровому образу жизни.
Ранние клинические и лабораторные признаки поражения почек часто бывают размытыми и не привлекают внимания врачей, особенно у пожилых пациентов. Эти начальные симптомы нередко воспринимаются как "возрастная норма."

Среди хронических неинфекционных заболеваний хроническая болезнь почек (ХБП) занимает особое место из-за своей широкой распространенности, значительного ухудшения качества жизни и высокого уровня смертности. На терминальной стадии ХБП требует дорогостоящих методов лечения, таких как диализ или трансплантация почки. Однако ни один из существующих методов заместительной терапии почек не является идеальным: они не могут полностью восстановить функцию почек и сопряжены с риском осложнений.

Ключевые слова: *Хроническая болезнь почек, гломерулосклероза, блокаторов кальциевых каналов, ремоделирования, дигидропиридин, лерканидипин.*

Rezume

XX-XXI asrning oxirida dunyo jamoatchiligi nafaqat tibbiy, balki katta ijtimoiy-iqtisodiy ahamiyatga ega bo'lgan global muammo – surunkali kasalliklar pandemiyasi bilan yuzlashdi. Qandli diabet, yurak, o‘pka va buyrakning surunkali kasalliklari, shuningdek, ularning turli kombinatsiyalari deyarli har bir odatda uchraydi. Yuqori texnologiyali intensiv va o‘rinbosar terapiya usullari inson hayotini saqlab qolishi mumkin bo‘lsa-da, ular har doim ham hayot sifatini yaxshilash, mehnat qobiliyatini saqlash va ijtimoiy faollikni tiklash imkonini bermaydi. Shu bilan birga, oddiy va arzon profilaktika choralari yetarlicha samarali qo‘llanmaydi, kasallik kech aniqlanadi va davolash jarayonida bemorlarning motivatsiyasi hamda sog‘lom turmush tarziga sodiqligi yetarli bo‘lmaydi.

Buyrak zararlanishining erta klinik va laboratoriya belgilari ko‘pincha noaniq bo‘lib, ayniqsa, keksa yoshdagi bemorlarda shifokorlar tomonidan e’tibordan chetda

qoladi. Bu esa buyrak kasalligining dastlabki belgilari “yoshga mos norma” sifatida qabul qilinishiga olib keladi.

Surunkali yuqumli bo‘lmagan kasalliklar ichida surunkali buyrak kasalligi (SBK) alohida o‘rin tutadi. Ushbu kasallik keng tarqalgan bo‘lib, hayot sifatining keskin pasayishiga, o‘lim ko‘rsatkichlarining yuqoriligiga olib keladi va terminal bosqichda qimmat terapiya usullari – dializ yoki buyrak transplantatsiyasini talab qiladi. Ammo buyrakni almashtirish terapiyasining mavjud usullari mukammal emas: ular yo‘qolgan buyrak funktsiyasini to‘liq tiklay olmaydi va asoratlar xavfini yuzaga keltiradi.

Kalit so'zlar: *surunkali buyrak kasalligi, glomerulosklerоz, kaltsiy kanallari blokatorlari, remodellashuv, digidropiridin, lerkanidipin.*

High-tech intensive and replacement therapies can save lives, but they do not always preserve the quality of life, work capacity, and social activity. At the same time, simple and affordable preventive measures are often applied ineffectively, diseases are detected late, and unfortunately, patients lack motivation and commitment to a healthy lifestyle. Early clinical and laboratory signs of kidney damage are often blurred and fail to alert doctors, especially in elderly patients. The initial symptoms of kidney disease are often considered part of the "age norm" (2).

The term "chronic kidney disease" (CKD) encompasses kidney damage or a reduction in glomerular filtration rate (GFR) below 60 ml/min/1.73 m² for more than three months, regardless of the initial diagnosis. This concept is based on the common pathophysiological mechanisms underlying the progression of pathological processes in kidney tissues, the shared risk factors for the development and progression of kidney diseases, and, consequently, the similarities in therapeutic and secondary prevention approaches (7).

To address these challenges, in 2002, the National Kidney Foundation (NKF) in the USA introduced the CKD concept with the participation of a large group of specialists (the K/DOQI — Kidney Disease Outcomes Quality Initiative Committee), including experts in nephrology, epidemiology, clinical medicine, and laboratory diagnostics. This concept is now widely accepted worldwide.

Remodeling is a complex process involving structural and geometric changes in vessels due to damage. Toxic factors, including metabolic effects, directly alter vascular structures and hemodynamic load. Changes in vascular structures lead to impaired function and blood supply to the respective organs. For this reason, studies have been conducted on the effect of calcium channel blockers (such as amlodipine and lercanidipine) on vascular remodeling in patients with CKD (4,6).

Among chronic non-communicable diseases, CKD holds a special place due to its high prevalence, severe deterioration of quality of life, and high mortality rates. In the terminal stage, it requires expensive treatment methods such as dialysis and kidney

transplantation. However, none of the available replacement therapies is perfect, as they fail to restore 100% kidney function and carry the risk of complications.

In cases of hypertension, the combination of arterial hypertension (AH) and CKD has a particularly unfavorable prognosis, as a reduction in GFR is not only a risk factor for CKD progression but also for cardiovascular mortality. Studies have confirmed that a decline in estimated GFR and albuminuria is associated with increased risks of cardiovascular death, CKD progression, and acute kidney injury.

Hypertension is one of the most common diseases affecting the cardiovascular system (9,11). According to epidemiological studies in our country, approximately 20-30% of the population suffers from hypertension. Prolonged elevated blood pressure can lead to target organ damage, including complications such as CKD. The risk of CKD development is three times higher in hypertensive patients compared to those with "optimal" blood pressure levels. Even patients with blood pressure in the range of 130–139/85–89 mmHg are 2.13 times more likely to develop microalbuminuria than those with normal blood pressure levels (12,13).

In hypertensive patients, vascular changes occur in the kidneys, including intimal thickening, fibrosis, thickening of arcuate and interlobular artery walls, and hyalinosis of arterioles. In the early stages of the disease, glomerular damage is localized, but in later stages, it is accompanied by atrophy and tubulointerstitial fibrosis (12).

The hemodynamic mechanisms of kidney damage during hypertension involve remodeling of the renal microcirculation, leading to ischemia due to glomerular hypoperfusion, glomerulosclerosis, and tubulointerstitial fibrosis. Elevated blood pressure disrupts the autoregulation of afferent arteriole tone, causing dilation and increased glomerular pressure. This disrupts glomerular hemodynamics, damages the membrane, and initiates a cascade of pathological changes leading to glomerulosclerosis (3).

At the subcellular level, calcium plays a dominant role in regulating the cardiovascular system (CVS). Calcium ions (Ca^{2+}), according to the biological "principle of uniformity of action," are critical in the functioning of various parts of the CVS: they regulate the excitation rhythm frequency of the heart pacemaker, the excitability of specialized heart cells, and the contractile function of myocytes—the structural cellular units of the CVS (15).

The International Society of Hypertension (ISH) has examined therapy standards for hypertension worldwide, involving 77 countries. A surprising consensus was revealed in treatment strategies for arterial hypertension: calcium antagonists, diuretics, and agents that block the angiotensin system are widely used across all countries. The criteria for initiating therapy, in almost all cases, were blood pressure values exceeding 140/90 mmHg (10).

Calcium influx is crucial for generating and maintaining the duration of action potentials, participating in pacemaker activity, and stimulating myocardial and smooth muscle cell contractions. Overall, calcium flux determines the chronotropic and inotropic effects on the heart's pumping activity and the tonic state of vascular walls. Particular attention is given to dihydropyridine drugs, which exhibit the most pronounced hypotensive effect (18).

The mechanism underlying this effect begins with the basal tone of smooth muscle cells, maintained by the constant slow influx of calcium through channels. "Calcium antagonists" bind to receptors on the inner surface of cell membranes, interacting most effectively in a depolarized state. This reduces calcium influx through the membrane, causing smooth muscle cell relaxation. The reduction in the constant slow influx of ions decreases basal tone: the vessel dilates, peripheral resistance decreases. This effect is independent of the etiology of arterial hypertension and is universal, as it primarily targets vascular tone itself (16).

The mechanism of action of calcium channel blockers has been well-studied and described in the works of domestic and foreign authors (e.g., Y.B. Belousov, V.S. Moiseev, V.K. Lepakhin, 1993; N.A. Andreev, V.S. Moiseev, 1995; Neyler W.G., 1993). In our review, we briefly note that the antihypertensive effect of calcium channel blockers is based on the non-competitive blockade of slow calcium channels in cardiomyocytes and smooth muscle cells of vascular walls. This leads to a sustained reduction in the tone of large arteries and arterioles, a decrease in total peripheral vascular resistance, and lower systolic and diastolic blood pressure (14).

A significant aspect of this drug group is its ability to prevent or slow vascular remodeling by reducing vascular wall stiffness, improving endothelial-dependent vasodilation via increased nitric oxide production (vasodilation) (5).

The nephroprotective effects of calcium channel blockers are achieved through the elimination of renal vasoconstriction, improved renal blood flow, increased glomerular filtration rate, and inhibition of mesangial cell proliferation mediated by hemodynamic and non-hemodynamic mechanisms. The changes in glomerular hemodynamics during calcium channel blocker administration are linked to their high antihypertensive activity and their selective ability to dilate afferent arterioles of the renal glomerulus, with minimal impact on efferent arterioles (7,9).

The diuretic and natriuretic effects of calcium channel blockers result from enhanced renal blood flow and direct promotion of sodium excretion in the tubules. Non-hemodynamic nephroprotective mechanisms of calcium channel blockers include improved endothelial function, reduced inflammatory and proliferative responses, antagonism to the mitogenic effects of platelet-derived growth factor and platelet-activating factor, suppression of mesangial cell proliferation, modulation of gene transcription involved in inflammatory changes, antioxidant effects, and inhibition of

endothelin-1—one of the factors involved in the progression of arterial hypertension (3).

L-type calcium channels are "slow" channels primarily localized in cardiomyocytes and the smooth muscle cells (SMCs) of vascular walls. Within the cardiovascular system, they maintain the electrical and mechanical activity of cardiomyocytes and vascular SMCs. These channels are one of the three types of calcium channels blocked by organic compounds, including dihydropyridines, benzothiazepines, and phenylalkylamines.

T-type calcium channels are "fast" channels primarily located in the heart's conduction system and neurons. They are almost unaffected by inorganic calcium channel antagonists. Under normal physiological conditions, calcium influx through these channels is regulated by neurotransmitters: adrenaline increases it (keeping the channels open), while acetylcholine decreases it (closing the channels). Excess Ca^{2+} influx or impaired calcium removal from cells disrupts their specific functions (conduction and contraction), leading to heart pump dysfunction or increased blood pressure (6,9).

Calcium influx is blocked by both inorganic ions (clinically insignificant) and organic compounds known as calcium channel antagonists. These drugs are widely used in clinical practice to treat patients with coronary artery disease (CAD), arterial hypertension (AH), and metabolic syndrome (MS), and to prevent vascular complications (1).

Recently, third-generation calcium channel blockers (CCBs) with high specificity and tissue selectivity for Ca^{2+} channels have been developed. These new drugs surpass their prototypes (first- and second-generation CCBs) in potency, duration of action, and high organ and tissue selectivity. The typical representatives of third-generation CCBs are amlodipine, lercanidipine, lacidipine, and manidipine, which have significant pharmacological properties for clinical practice:

- High bioavailability (60–80%) and minimal fluctuations in plasma concentrations throughout the day, ensuring predictable efficacy.
- High vascular selectivity, minimizing the effects on myocardial contractility, sinus node function, and atrioventricular (AV) conduction.
- Long-lasting biological effects (24–36 hours), eliminating the need for extended-release formulations (5).

Third-generation CCBs differ in physicochemical properties, determining the uniqueness of their pharmacodynamic and pharmacokinetic clinical effects. For instance, amlodipine has a long half-life, maintaining high plasma concentrations. It gradually diffuses into the bilayer of smooth muscle cell membranes in arteries, binding to L-type calcium channels and blocking their functional activity. This explains the prolonged antihypertensive effect compared to other CCBs (8).

Achieving target blood pressure levels is crucial to slowing the progression of renal dysfunction, microalbuminuria, and proteinuria. L-type calcium channel blockers with additional nephroprotective properties can be used to achieve these goals (17).

It is important to note that modern therapy for arterial hypertension is not limited to lowering blood pressure. The new generation of antihypertensive drugs generally offers a range of organ-protective effects, and lercanidipine is no exception. Below are some recent findings related to its anti-inflammatory, antioxidant, nephroprotective, antidiabetic, and other properties.

Israeli researchers (Farah et al.) studied new mechanisms in the development of essential arterial hypertension. Insulin resistance, inflammation, and free radical damage significantly contribute to hypertension. A positive correlation was found between the activity of polymorphonuclear leukocytes (which release superoxide anions), their calcium content, and the degree of insulin resistance. After two months of lercanidipine use, a significant reduction was observed in polymorphonuclear leukocyte apoptosis, C-reactive protein levels, total leukocyte count, and serum insulin levels. The authors concluded that this drug is indicated for patients with arterial hypertension not only for its hypotensive effect but also for its impact on comorbid conditions such as diabetes and atherosclerosis (14).

The nephroprotective properties of calcium channel blockers have been reported. In experiments on acute kidney injury, increased levels of superoxide dismutase and glutathione peroxidase, along with decreased malondialdehyde levels, were observed in renal tissues after drug administration. This demonstrates the hidden positive attributes of these drugs, which contribute to their beneficial effects (8).

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