METABOLIC NEUTRAL NEPHROPROTECTIVE ANTIHYPERTENSIVE DRUGS: BETA BLOCKERS AND CALCIUM CHANNEL BLOCKERS

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Abstract

Although the response to antihypertensive therapy is individual, almost all antihypertensives reduce arterial pressure by 10-15%. From the analysis of the effectiveness of antihypertensives, both in monotherapy and comedication in patients with multiple comorbidities, through clinical studies and real-world data, it is concluded that beta blockers and calcium channel blockers have been proven to be effective and safe in all groups of patients. This comprehensive efficacy, with the optimal profile of side effects, results from proven efficacy in primary and secondary prevention of adverse cardiovascular events, impact on the sympathetic nervous system with nephroprotection, and metabolic neutrality.

Keywords: antihypertensive drugs, beta blockers, calcium antagonists, metabolic neutrality, nephroprotection

Introduction

The influence of pulse blood flow is pathoanatomically reflected in changes in the endothelium and remodeling or hypertrophy of smooth muscle cells[1]. In patients with hypertension, the accumulation and oxidation of LDL cholesterol are greatest in the zone of turbulent flow with altered stress and biomechanical stress in the arterial wall[1]. Although the response to antihypertensive therapy is individual, almost all antihypertensive drugs reduce arterial blood pressure (BP) by at least 10-15% (except in black race), as shown in table 1[2, 3]. The therapeutic algorithm in the treatment of hypertension is influenced, among other things, by the patient's comorbidities (table 2)[2, 3].

Table 1. Individual response to certain antihypertensive drugs

Group of antihypertensive drugs	Response to therapy (BP reduction in %)
Thiazide diuretics	50-55
Beta blockers	45-50
Ca channel blockers	40-60
ACE inhibitors	50-60
Alpha-blockers	35-40
Central agonists	30-35

Table 2. Combinations of antihypertensive drugs in patients with multiple comorbidities[2, 3]

Hypertension and Comorbidities	Combination of antihypertensive drugs
Angina pectoris	BB or CCB
Previous myocardial infarction	BB, ACE, or AT1B
Heart failure	BB, ACE or AT1B, diuretic
Renal failure	ACE or AT1B, CCB, diuretic
Peripheral arterial disease	CCB, ACE, or AT1B
Prostatic disease	Alpha blockers
Metabolic syndrome	ACE or AT1B, CCB
Diabetes mellitus	ACE or AT1B, CCB

Legend: **BB** - beta blocker; **CCB** - calcium channel blocker; **ACEi** - angiotensin-converting enzyme inhibitor; **ARBs1** - angiotensin 1 receptor blockers

Through clinical studies, the effectiveness and safety of these drugs in all groups of patients have been proven, and through daily clinical practice, confirmed, not only as antihypertensives but also as etiological therapies of various cardiovascular entities, with a favorable influence on the sympathetic nervous system, nephroprotection and metabolic neutrality[1-3].

Metabolically neutral antihypertensive nephroprotective drugs: beta blockers

There are clear recommendations from cardiology associations that blood pressure checking should always be followed by heart rate measures, because the value of heart rate at rest is an independent predictor of cardiovascular disease and death in various conditions, including hypertension[3]. Beta blockers are not a homogeneous class. The main factors in determining the diversity of beta blockers are beta selectivity, vasodilatory properties, metabolic profile, side effects, and efficacy[3]. The most important

characteristic of this group of drugs is their cardioselectivity, which is selective binding to ß1 receptors in the heart and kidneys. Bisoprolol and nebivolol have the highest cardioselectivity, followed by metoprolol, which also binds to ß2 receptors (smooth muscles of airways and blood vessels), and carvedilol, which is a partial antagonist of alpha receptors, has the lowest cardioselectivity[3]. Special attention should be paid to patients with pulmonary comorbidities because they usually already have some of the ß2 agonists in therapy so there is no paradoxical combination of ß2 agonists and antagonists (table 3).

Table 3. Agonists of beta-adrenergic receptors

Agonists of beta-adrenergic receptors	Receptors	Agonist
Non-selective	ß1 and ß2	Adrenaline
Selective	ß2	long (slow) acting (salmeterol, formoterol)
		short (fast) acting (salbutamol, terbutaline and fenoterol)

Considering that in 60% of patients with first-degree hypertension, damage to target organs (heart, brain, kidneys) has already occurred, the vasodilatory effect of beta blockers is significant in defining the therapeutic algorithm[3-4]. Nitric oxide-mediated vasodilatation is physiologically based on a reduction in peripheral resistance. Nebivolol has this characteristic of the cardioselective beta blockers, which not only has a sustainable effect on slowing down the heart rate and a favorable so-called "trough/peak" ratio (an index that expresses the consistency in blood pressure regulation between two doses of the drug) but also has the property that, through a vasodilatory effect on blood vessels, it reduces the stiffness of arteries with a potential anti-atherosclerotic effect. The anti-atherosclerotic effect of beta blockers is manifested by slowing down the formation of atheromatous plaque[3, 5-8].

In addition to improving endothelial dysfunction, which is particularly important in patients with diabetes, where extensive angiopathy occurs due to microvascular complications of diabetes, favorable metabolic profile of the drug, was noted, without the risk of developing diabetes, and a significantly lower risk of developing insulin resistance compared to metoprolol (ß1 and ß2 antagonists)[3, 6-9]. Metabolic neutrality is a feature of both nebivolol and another cardioselective beta blocker, bisoprolol. Apart from metabolic neutrality and a dose-dependent effect sustained over time, bisoprolol is effective in all age groups, with a measurable effect on the regression of left ventricular hypertrophy in patients with hypertensive heart damage[3, 8, 9].

The nephroprotective effect of third-generation beta blockers such as nebivolol and carvedilol derives not only from their antihypertensive effect achieved by blocking adrenergic receptors but also from vasodilatation mediated by nitric oxide of nebivolol and the antioxidant effect of carvedilol through the suppression of oxidative stress in the glomeruli, proximal kidney tubules and the surrounding interstitial tissue[10, 11]. A recent study on an animal model highlights the effectiveness of nebivolol in the treatment of antiviral-induced nephropathy in terms of partial recovery of glomerular filtration rate (GFR), renal damage expressed through albuminuria, normalization of blood pressure, and reduction of the degree of vasoconstriction of renal blood vessels, and potential new indications in the human population for this group of beta blockers[12].

Metabolically neutral antihypertensive nephroprotective drugs: calcium channel blockers

Calcium channel blockers (calcium antagonists) can be divided into three large groups: phenyl alkylamines (verapamil), benzothiazepines (diltiazem), and dihydropyridines (nifedipine, amlodipine, felodipine, isradipine, nicardipine, lercanidipine, clevidipine)[13]. Nifedipine and other dihydropyridines primarily act as vasodilators, while verapamil and diltiazem block calcium channels in the myocardium as well. Due to these differences, dihydropyridines are primarily used as antihypertensive agents, while verapamil and diltiazem, due to their more pronounced suppression of SA node automaticity and AV conduction, are also used as antiarrhythmics[13]. The first generation of dihydropyridines is represented by nifedipine; a typical representative of the second generation is amlodipine, while the third generation is represented by lercanidipine (table 4).

By improving the dihydropyridine molecules, their clinical efficiency and tolerability are improved[12-14]. Calcium antagonists of the dihydropyridine structure are characterized by selective and gradual inhibition of the transmembrane influx of calcium ions (in vascular smooth muscles, cardiac muscle, and other smooth muscles). The selectivity is reflected in a greater effect on the cells of the vasculature, than on the cells of the heart muscle, without affecting the concentration of calcium ions in the serum. Inhibition of calcium channels is characterized by a gradual onset of action, so the problem of reflex tachycardia as a complication of treatment, which previously affected patient adherence, was overcome with new formulations of calcium antagonists[14]. The highest vascular selectivity is based on the targeted effect on arterial blood vessels[14, 15]. High selectivity for vascular tissue is accompanied by the absence of negative inotropic action, with gradual onset of action and prolonged action[14]. Age does not affect the pharmacokinetics of calcium antagonists of the dihydropyridine structure. These drugs are characterized by a double elimination route (through the kidneys and liver) and have no significant interaction with other drugs[13, 15]. In addition to a gradual and uniform antihypertensive effect, compared to other classes of antihypertensives, calcium antagonists of the newer

Table 4. Three generations of dihydropyridine calcium antagonists

Dihydropyridine calcium antagonists	Representers	Characteristics
I generation		Short acting
	Nifedipine retard	Long-acting-modification of resorption at the GIT
II generation	Nicardipine Nitrendipine Nisoldipine Nimodipine Isradipine Amlodipine	Long-acting-prolonged plasma half-life
III generation	Lacidipine Lercanidipine Klevidipine	Long-acting-prolonged, half-life at the receptor level No significant interactions with other drugs Pharmacokinetic characteristics independent of the patient's age Lower incidence of leg edema Reduction of the appearance of redness Reduction of headache and itching

generation show a favorable trend when it comes to the regression of left ventricular hypertrophy (LVH) as part of hypertensive heart damage. Compared to losartan, lercanidipine resulted in a more significant decrease in LVH[3, 15].

The expected side effects of treatment with conventional calcium receptor antagonists (leg edema, redness, headache, and itching) arise from the fact that they only dilate the arterioles, increasing the pressure in the capillaries, which all results in the appearance of swelling, petechiae, and hyperpigmentation. Also, dihydropyridine calcium antagonists of the first and second generation (nifedipine, amlodipine) cause vasodilation of afferent arterioles and an increase in capillary pressure in the glomeruli with consequent glomerular damage[12, 13]. The LEAD study compared the effects of three dihydropyridine calcium antagonists: lercanidipine, felodipine, and nifedipine GITS (in the form of a gastrointestinal therapeutic system), on blood pressure and heart rate in 325 patients with mild to moderate hypertension, aged 35-74 years. After 8 weeks of therapy, no significant differences in blood pressure changes were observed between the three groups. The incidence of adverse drug reactions was lower in the group of patients treated with lercanidipine and nifedipine than in the group of patients treated with felodipine. At the end of the study, 89% of patients reached their target blood pressure values. Its action starts slowly, which makes it possible to avoid reflex tachycardia, which is associated with the use of dihydropyridine[16]. Lercanidipine dilates both arterioles and venules and does not cause an increase in capillary pressure and consecutive events. Over 8 weeks, amlodipine led to a significant increase in leg volume, unlike lercanidipine[3, 16]. In the Lercanidipine Challenge Trial, introducing lercanidipine instead of amlodipine, side effects were reduced, namely lower leg swelling by 46%, facial flushing by 51%, headache, and rash by 53%, and the frequency of dizziness by 26%. By returning to the initial therapy-rechallenge, all side effects increased to initial values[3, 16, 17]. Through vasodilatation of afferent and efferent arterioles, lercanidipine reduces capillary pressure in the glomeruli, which is accompanied by a reduction in albuminuria and a significant nephroprotective effect[17]. Given the significantly lower risk of vasodilator side effects at high doses compared to amlodipine and nifedipine, patient compliance with lercanidipine was at least 25% higher than with other calcium channel blockers[18]. Lercanidipine is metabolically neutral, does not change biochemical parameters (glycemia, creatinine, total cholesterol), and does not affect the patient's lipid profile[3, 16-18].

Moreover, recent studies suggest a potentially positive metabolic effect of lercanidipine in terms of improving parameters of lipid status (total, LDL and HDL cholesterol, triglycerides, apo A-I and apo B) as a long-term effect, in addition to antihypertensive, while in patients with diabetes, it showed a beneficial effect on glycoregulation in the sense of reducing blood glucose and glycosylated hemoglobin, independent of the dose[3, 16-19]. In addition to the effective reduction of systolic and diastolic blood pressure in patients with systolic/diastolic hypertension, it provides blood pressure control for more than 24 hours, without a negative inotropic effect (contractility) with a homogeneous distribution of the antihypertensive effect. It is proven to be an advantage in patients with isolated systolic hypertension and patients with diabetes since it provides protection against hypertensive organ damage and allows combining it with other drugs[17-19].

In the elderly, an increase in peripheral vascular resistance was recorded, along with a decrease in the number and caliber of arterioles[19]. Therefore, the antihypertensive therapy of the elderly must be adapted to the slower response of baroreceptors and the adrenergic system, worsened cerebral autoregulation as well as frequent comorbidities[3, 19]. In addition to hypertension, in the elderly, the use of calcium channel blockers as an antihypertensive favors the existence of isolated systolic hypertension, angina pectoris, and coronary or carotid atherosclerosis, with some effectiveness of lercanidipine and amlodipine in chronic therapy[3, 20]. The effectiveness of lercanidipine in the regulation of systolic and diastolic arterial hypertension has been confirmed in subgroups of patients with diabetes and patients with chronic renal failure[3, 19-21]. In patients with chronic renal failure, lercanidipine led to a significant reduction in arterial pressure, as well as an improvement in creatinine clearance and a reduction in proteinuria[3, 21].

Conclusion

Beta blockers and calcium antagonists have been proven to be effective and safe in all patient groups. This comprehensive effectiveness, along with an optimal profile of side effects, enables their use in primary and secondary prevention of unwanted cardiovascular events, which is followed by a favorable effect on the sympathetic nervous system with nephroprotection and metabolic neutrality.

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