The choice of the antihypertensive drug in special conditions: evidence-based data in co-morbid hypertension and metabolic disorders (part 3)

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Abstract
The article reviews the main approaches to the hypertension management in metabolic disorders, including diabetes, dyslipidemia, hyperuricemia and gout, as well as in sleep apnea. The data are based on the guidelines by the Joint National Committee of the USA, European Society of Cardiology/European Society of Hypertension, American Society of Hypertension/International Society of Hypertension, considering the important issues mentioned in national guidelines by Russian Society of Cardiology.

Key words: hypertension, diabetes mellitus, metabolic syndrome, gout, sleep apnea, electrolyte imbalance.

Выбор антигипертензивного препарата в особых группах пациентов: данные доказательной медицины при сочетании артериальной гипертензии и метаболических нарушений (часть 3)

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Резюме
Данная статья посвящена особенностям лечения артериальной гипертензии и выбору антигипертензивного препарата у пациентов с артериальной гипертензией в сочетании с нарушениями обмена углеводов, липидов, пуриновых оснований и электролитов, а также нарушениями ды-

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хания во время сна. В статье суммированы основные данные, представленные в рекомендациях по диагностике, ведению и лечению артериальной гипертензии Объединенного национального комитета США, Европейского общества кардиологов и Европейского общества по артериальной гипертензии, Американского и Международного обществ по артериальной гипертензии с учетом национальных рекомендаций Российского кардиологического общества.

Ключевые слова: артериальная гипертензия, сахарный диабет, метаболический синдром, подагра, апноэ во время сна, электролитные нарушения.

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Introduction

This review is the next part in a series of articles that discusses the similarities and differences in guidelines of various societies of cardiology [US Joint National Committee (JNC8), European Society of Cardiology and the European Society of Hypertension (ESC/ESH), the American and the International Society of Hypertension (ASH/ISH), the Russian society of Cardiology (CSC)]. It addresses questions of hypertension (HTN) treatment in patients with concomitant metabolic disorders — metabolic syndrome or its components, diabetes mellitus (DM), hyperuricemia and gout [1–7], as well as disorders of mineral exchange. Although general recommendations are applicable in hypertensive patients with various metabolic disorders and commonly co-existing sleep-disordered breathing admitting the use of any class of antihypertensive drugs [thiazide/thiazide-like diuretics, calcium channel blockers, angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers II (ARB)], in some cases, the choice of a particular therapeutic approach may have both advantages and disadvantages. The review will cover issues of choice of the antihypertensive drug in patients with concomitant metabolic disorders.

Obesity and dyslipidemia

Worldwide experts agree that lifestyle modification is essential in people with metabolic disturbances, metabolic syndrome or its components. First of all, it includes weight reduction and the increase of physical activity, which contributes to blood pressure control (BP), improvement of metabolic parameters, prevention or delay of DM development. In addition, it is necessary to control risk factors such as dyslipidemia and hyperglycemia by both lifestyle modification and drug therapy [1–4].

However, if non-pharmacological methods are inefficient (typically assessed within 3 months or more) and BP is maintained above 140/90 mm Hg, antihypertensive therapy should be started in persons with metabolic disorders. The target BP level in this group is less than 140/90 mm Hg [3]. Blockers of the renin-angiotensin-aldosterone system (RAAS) and calcium channel blockers are preferred due to their favorable (or at least neutral) effect on insulin sensitivity. At the same time, beta-blockers (except drugs with vasodilating properties) and diuretics should be used as additional therapy, at low doses due to their unfavourable effects on carbohydrate and lipid metabolism.

In coexistent HTN and metabolic syndrome centrally acting drugs (as adjunction therapy) are reasonable (regarding pathogenesis), especially highly specific agonists of I1-imidazoline receptors (moxonidine and rilmenidine) in view of their metabolic neutrality and sympatholytic activity [8–10].

Type 2 diabetes mellitus and other carbohydrate metabolism disturbances

There is no disagreement between experts of various medical societies that diabetic patients require antihypertensive treatment at systolic BP $\geq$ 140 mm Hg [1–4]. Renoprotective drugs are preferable if there are signs of nephropathy, particularly with microalbuminuria [1, 3]. However, diabetic retinopathy and/or neuropathy without HTN is not an indication for antihypertensive therapy, which will not help its reverse development [3].

Also, most experts agree that the target BP level in diabetic patients is SBP < 140 mm Hg. (as in the general population of hypertensive patients) and DBP < 80–85 mm Hg [1–5]. At the same time, according to the experts of the World Health Organization and the American Heart Association BP should be maintained at the level

of 125–130 mm Hg for SBP and 70–75 mm Hg for DBP in diabetic patients [11]. However, there is no definitive evidence of the feasibility of BP reduction below 130/80 mm Hg. The SBP reductions less than 130 mm Hg currently seems unreasonable considering the absence of additional beneficial effects [1–3]. Treating patients with DM J-shaped curve phenomenon should be always considered. It illustrates the fact that excessive BP reduction can lead to vital organs hypoperfusion. This effect may have irreversible consequences and increase the risk of cardiovascular complications that is even higher in presence of diabetes-associated micro- and macroangiopathy [3].

In order to reduce BP in patients with DM any class of antihypertensive drugs can be used. This view is supported by the majority of the recommendations [1–4]. According to all experts, combined antihypertensive therapy is justified in diabetic patients due to the difficulties in achieving target BP level in these patients. The rational combination should demonstrate renoprotective effects and include an ACE inhibitor or ARB [1–4]: RAAS blocker + slow calcium channel blockers, RAAS blocker and + thiazide or thiazide-like diuretic. However, it is necessary to avoid simultaneous administration of two or more RAAS blockers (including aliskiren — renin inhibitor) due to the increased risk of unfavorable outcomes [3, 12]. The risk of hyperkalemia should be considered, especially when ARB are prescribed [1, 4]. In the African-American population initial therapy should include slow calcium channel blockers or thiazide/thiazide-like diuretics [1, 2].

Regarding potential worsening of glucose metabolism in patients with hypokalemia, a combination of thiazide/thiazide-like diuretic and potassium-conserving drugs (or RAAS blockers) [1, 3, 4].

Beta-blockers could potentially increase the risk of developing/aggravation of insulin resistance, and then used in combination therapy. Beta-blockers are considered to be the most reasonable in patients with coronary heart disease (CHD) or chronic heart failure (CHF). American experts recommend avoiding the combination of beta-blockers and thiazide/thiazide-like diuretics in patients with known DM and in subjects with high risk of glucose metabolism disorders. Beta-blockers should be avoided in patients with HTN and DM with a tendency to hypoglycemia (especially in insulin-dependent DM or treated with other antidiabetic drugs) due to their ability to mask the symptoms of hypoglycemia and prevent timely treatment.

In co-existing HTN and DM drugs with central action (as adjunction therapy) are pathogenetically justified, especially highly specific agonists I1-imidazoline receptors (moxonidine and rilmenidine) because of their beneficial effect on glucose metabolism and insulin sensitivity [8–10].

ASH-ISH recommendations indicate the feasibility of a combination of diuretics and alpha-blockers in some cases (resistant HTN and DM or high risk of glucose metabolism disturbances) due to their beneficial effects on glucose metabolism. American experts do not recommend to assign alpha-blockers as first-line therapy, emphasizing that the choice of antihypertensive medication in patients with DM should be in accordance with general principles applied in general population [1].

Patients with glucose metabolism disturbances require a complex approach (including non-drug methods). Therapy should address BP control, as well as glycemia, too; although the target level of glycated hemoglobin (< 9%, ≤ 7% or lower) remains disputable [13, 14].

Hyperuricemia and gout

A common coexistence of hyperuricemia, with HTN, renal blood flow reduction and nephrosclerosis require routine monitoring of the uric acid level in patients with HTN [15]. Patients with HTN have high risk of gout developing. Moreover, hyperuricaemia is a risk factor for cardiovascular complications and population disability. Persistent increase in uric acid level above the normal range (> 420 mmol/L for men, > 340 mmol/L for women) requires cautious administration of diuretics, especially thiazide and thiazide-like diuretics. In case of clinical manifestations of gout, all diuretics are contraindicated because all of them inhibit the excretion of uric acid and lead to hyperuricemia. β-blockers cannot be considered the drugs of choice, as they promote hyperuricemia by increasing insulin resistance and hyperinsulinemia.

In patients with gout and HTN calcium antagonists and ACE inhibitors are drugs of choice, because they do not exacerbate hyperuricemia. Also Losartan (a representative of the ARB class) is the drug of choice due to the beneficial effect on purine metabolism and uric acid reduction. At prolonged use it reduces the risk of gout development, which can be explained by higher urate excretion due to the reduction of its reabsorption in the proximal kidney tubules. At the same time, this effect is less pronounced or absent in other drugs of this class, and their long-term use may be associated with increased risk of gout development [16]. Alpha-1-blockers, in particular, doxazosin can be used in people with gout and HTN.

A complex approach to the patient with HTN and gout should also include non-drug activities (first of all, a diet with purine-containing food restriction). Therefore, drugs reducing uric acid level should be administered in complex treatment of gout (without exacerbations — xanthine oxidase inhibitors such as allopurinol and febuxostat, in resistant forms — intravenous peglotikazy, during an exacerbation — colchicine), because gout remission and decline in uric acid contribute to BP control [17].

A mineral metabolism disturbance

Most of the antihypertensive agents are involved in the electrolytes exchange that implies a differentiated approach in patients with known concomitant disorders of mineral metabolism.

Disturbances of calcium-phosphorus metabolism and osteoporosis

There is no doubt, that known or suspected mineral metabolism disturbances require a complex approach involving endocrinologists and other specialists, non-pharmacological and pharmacological correction of comorbid conditions, additional therapy, aimed at restoring calcium, vitamins D and K levels, normalization of salt intake, preventing loss of bone (bisphosphonates and other), etc. Nevertheless, antihypertensive therapy itself has an impact (both favorable and negative) on the development of calcium-phosphorus metabolism disorders.

Among all antihypertensive drugs only thiazide diuretics have proven beneficial effects on the conservation (and according to some data, even increasing) of bone mineral density (due to the stimulating effect on osteoblast differentiation and calcium intake in the bone, as well as increased calcium absorption in the gastrointestinal tract and effect on calcium reabsorption in the distal convoluted tubules of the kidneys). Thus, these are advisable drugs in patients with known osteopenia and osteoporosis. Similarly, aldosterone antagonists potentially have an indirect calcium-saving effect and help to preserve bone mineral density (for aldosterone receptor antagonists such effects are not demonstrated).

At the same time, loop diuretics can worsen hypocalcemia and bone remodeling.

In patients with *hyperoxaluria*, which is characterized by impaired metabolism of oxalic acid and is accompanied by increased production of calcium oxalate and its release in the urine, loop diuretics are also inappropriate. At the same time, thiazide and thiazide-like diuretics may have a beneficial effect by reducing urinary calcium and calcium salt crystallization.

The data about other antihypertensive drugs are more contradictory. RAAS blockers are supposed to contribute to the increase in bone mineral density due to the impact on the local bone RAAS system and preventing of osteoclasts activation. Mostly these effects are attributed to ACE inhibitors. ARBs have similar effect, although the data are scarce. Selective beta-blockers are associated with higher rates of bone mineral density and a lower risk of bone fractures. Despite the active intervention in calcium intracellular metabolism, calcium channel blockers do not significantly affect bone mineral density, and nowadays their neutral effect on the osteoporosis development and fracture risk is recognized. Alpha-blockers are not recommended, because they may indirectly contribute to increase of falls and fracture risk, although data about their direct impact on mineral metabolism are absent [18–20].

Sodium metabolism and "salt-sensitive"

Low-salt diet is one of the first non-drug approaches recommended to a hypertensive patient and recognized worldwide. This reflects the understanding of the sodium chloride role and fluid retention in the development of a persistent BP increase [1–4]. At the same time it is known, that "salt-sensitive" people are more prone to

the consequences of excessive salt intake than "salt-resistant" subjects. "Salt-sensitivity", caused by genetic factors, might be assumed in patients with mostly higher systolic BP, in elderly persons, in patients with metabolic disorders and kidney damage. The following methods are used to determine salt sensitivity: salt taste threshold assessment and sodium excretion in saliva and urine. Furthermore, the estimation of plasma renin activity (PRA) may help to identify HTN associated with fluid and sodium retention in the organism, and to the choice of the antihypertensive drug. The PRA level less than 0.65 ng/mL/h in an untreated patient proves low-renin (volume-dependent) HTN and high sodium concentration. In this case, natriuretic drugs are the most efficient. This group includes all diuretics, aldosterone receptor blockers, calcium channel blockers and alpha-blockers [1–4, 21–23].

Obstructive sleep apnea (OSA)

Obstructive sleep apnea (OSA) is a recognized risk factor for HTN (according to the ESH guidelines, OSA is one of the reasons of true resistant HTN; at the same time American experts included OSA in the list of secondary HTN reasons). Therefore, OSA should be considered in approach to a hypertensive patient [1–3, 24, 25]. For clinical practice it is important to distinguish OSA as a finding by the sleep study, and obstructive sleep apnea syndrome, which is a combination of OSA and clinical symptoms (severe daytime sleepiness, unexplained by other causes, and/or two of the following signs: attacks of dyspnea during sleep, repeated arousals at night, unrefreshing sleep, daytime fatigue and impaired attention focusing) [24, 25]. Sleep-disordered breathing may promote the development of hypertension regardless of the subjective complaints. This requires further study, even in asymptomatic patients.

Currently, there is no clear data about benefits of any antihypertensive drugs classes in patients with HTN and OSA. Considering pathogenesis, drugs with sympatholytic action, including RAAS blockers, centrally acting drugs (first of all high specific agonists of I1-imidazoline receptors) are reasonable [8–10, 26]. Regarding frequent co-existence of OSA and metabolic disorders, beta-blockers, diuretics may be limited to low doses and metabolically neutral representatives (high selective beta-blockers, thiazide diuretics and aldosterone antagonists, which demonstrated high efficacy in patients with HTN and OSA) [24, 25].

Lifestyle modification should be actively promoted among hypertensive patients with obstructive breathing disorders. First of all, it includes weight loss and an increase of aerobic exercise, which helps to reduce BP, as well as the decrease of SDB severity. Postural treatment should be considered especially in patients with position-dependent OSA (most commonly associated with supine position). The most available method is fixing (on the back) of a circular object (e. g. tennis ball) or other form of accessory that will prevent overturning in this position during sleep. Other recommendations should include avoidance of alcohol, especially 4–5 hours before bedtime; avoidance of hypnotics, as well as any drugs with myorelaxant action (especially at night), as they can aggravate sleep breathing disorders.

Approaching a hypertensive patient with OSA, pathogenetic treatment should be considered, in particular, non-invasive ventilation. Although data of its effect on BP is still controversial, and the degree of BP reduction during treatment does not exceed 2 mm Hg according to a meta-analysis. It may be associated with several factors, such as insufficient duration of therapy, poor compliance, lack of efficiency in some cases, that requires careful monitoring and control. Therefore, currently there is no clear opinion whether treatment (as well as other types of adjuvant therapy of OSA, such as oral appliances) is indicated only to reduce BP in patients with OSA [3, 24, 25].

Conclusions

Patients with HTN and various metabolic disorders or apnea require complex treatment. Non-pharmacological activities aimed at lifestyle modification should be an essential part. These are weight reduction, increased physical activity, as well as approaches contributing to the normalization of comorbid condition (glycemic control, lipid metabolism, non-invasive ventilation, etc.). When drug therapy is prescribed metabolically neutral drugs should be preferred, such as RAAS blockers, calcium channels blockers, in some cases, centrally acting drugs (selective agonists of I1-imidazoline receptors) and alpha-blockers

(as additional agents). At the same time, other classes of antihypertensive drugs (beta-blockers, diuretics, etc.) should be used in the treatment of patients with metabolic disorders and co-existent, ischemic heart disease or heart failure.

Conflict of interest

The authors declare no conflicts of interest.

References

1. James PA, Oparil S, Carter BL et al. 2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults Report From the Panel Members Appointed to the Eighth Joint National Committee (JNC 8). J Am Med Assoc. 2014;311(5):507–520.

2. Weber MA, Schiffrin EL, White WB et al. Clinical practice guidelines for the management of hypertension in the community a statement by the American society of hypertension and the International society of hypertension. J Hypertens. 2014;32(1):3–15.

3. Mancia G., Fagard R., Narkiewicz K. et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertens. 2013;31(7):281–357.

4. National guidelines on cardiovascular prevention. Cardiovascular Therapy and Prevention. Kardovskuliarnaia Terapiia i Profilaktika. 2011;10(6):64. [In Russian].

5. Baranova EI. Treatment strategies of arterial hypertension in special conditions (2013 European Society of Hypertension and European Society of Cardiology guidelines for the management of arterial hypertension). Arterial'naya Gipertenziya = Arterial Hypertension. 2014;20(1):38–44. [In Russian].

6. Korostovtseva LS, Zvartau NE, Konradi AO. The choice of the antihypertensive drug in special conditions: evidence-based data in co-morbid cardiovascular diseases. Arterial'naya Gipertenziya = Arterial Hypertension. 2014;20 (3):147–151. [In Russian].

7. Avdonina NG, Korostovtseva LS, Irtyuga OB, Zvartau NE, Konradi AO. The choice of the antihypertensive drug in special conditions: gender- and age-related differences. Arterial'naya Gipertenziya = Arterial Hypertension. 2014;20(4):232–237. [In Russian].

8. Chrisp P, Faulds D, Moxonidine. A review of its pharmacology, and therapeutic use in essential hypertension. Drugs. 1992;44:993–1012.

9. Haenni A, Lithell H. Moxonidine improves insulin sensitivity in insulin-resistant hypertensives. J Hypertens. 1999;17(3):29–35.

10. Kaan EC, Bruckner R et al. Effects of agmantine and moxonidine on glucose metabolism: an integrated approach towards pathophysiological mechanisms in cardiovascular metabolic disorders. Cardiovasc Risc Factors. 1995;5(1):19–27.

11. Chobanian AV, Bakris GL, Black HR et al. Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure. National Heart, Lung, and Blood Institute, National High Blood Pressure Education Program Coordinating Committee. Seventh report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure. Hypertension. 2003;42:1206–1252.

12. Parving HH, Brenner BM, McMurray JJV, de Zeeuw D, Haffer SM, Solomon SD. Cardiorenal endpoints in a trial of aliskiren for type 2 diabetes. N Engl J Med. 2012;367:2204–2213.

13. Gerstein HC, Miller ME, Byington RP, Goff DCJr, Bigger JT, Buse JB et al. Effects of intensive glucose lowering in type 2 diabetes. Action to Control Cardiovascular Risk in Diabetes Study Group. N Engl J Med. 2008;358 (24):2545–2559.

14. Eeg-Olofsson K, Cederholm J, Nilsson PM, Zethelius B, Svensson AM, Gudbjörnsdóttir S et al. Glycemic control and cardiovascular disease in 7,454 patients with type 1 diabetes: an observational study from the Swedish National Diabetes Register (NDR). Diabetes Care. 2010;33 (7):1640–1646.

15. Choi HK, Atkinson K, Karlson EW, Curhan G. Obesity, weight change, hypertension, diuretic use, and risk of gout in men: the health professionals follow-up study. Arch Intern Med. 2005;165(7):742–748.

16. Choi HK, Soriano LC, Zhang Y, García Rodríguez LA. Antihypertensive drugs and risk of incident gout among patients with hypertension: population based case-control study. Br Med J. 2012;344: d8190.

17. Hamburger M, Baraf HS, Adamson TC, Basile J, Bass L, Cole B et al. 2011 recommendations for the diagnosis and management of gout and hyperuricemia. Phys Sportsmed. 2011;39(4):98–123.

18. Ghosh M, Majumdar SR. Antihypertensive medications, bone mineral density, and fractures: a review of old cardiac drugs that provides new insights into osteoporosis. Endocrine. 2014;46(3):397–405.

19. Kanis JA, McCloskey EV, Johansson H, Cooper C, Rizzoli R, Reginster JY. Scientific Advisory Board of the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) and the Committee of Scientific Advisors of the International Osteoporosis Foundation (IOF)European guidance for the diagnosis and management of osteoporosis in postmenopausal women. Osteoporos Int. 2013;24(1):23–57.

20. Ilić K, Obradović N, Vujasinović-Stupar N. The relationship among hypertension, antihypertensive medications, and osteoporosis: a narrative review. Calcif Tissue Int. 2013;92(3):217–227.

21. Hajjar I, Kotchen TA. Trends in prevalence, awareness, treatment, and control of hypertension in the United States, 1988–2000. J Am Med Assoc. 2003;290 (2):199–206.

22. Egan BM, Basile JN, Rehman SU, Davis PB, Grob CH, Riehle JF et al. Plasma renin test- guided drug treatment algorithm for correcting patients with treated but

uncontrolled hypertension: a randomized controlled trial. Am J Hypertens. 2009;22(7):792–801.

23. Kotovskaya YV, Kravtsova OA, Pavlova EA. Plasma renin assessment as the strategy of hypertension management. Arterialnaya Gipertenziya = Arterial Hypertension. 2013;19 (5):380–388. [In Russian].

24. Parati G, Lombardi C, Hedner J, Bonsignore MR, Grote L, Tkacova R. Position paper on the management of patients with obstructive sleep apnea and hypertension: joint recommendations by the European Society of Hypertension, by the European Respiratory Society and by the members of European COST (Co-operation in Scientific and Technological research) ACTION B26 on obstructive sleep apnea. J Hypertens. 2012;30:633–646.

25. Parati G, Lombardi C, Hedner J, Bonsignore MR, Grote L et al. Recommendations for the management of patients with obstructive sleep apnoea and hypertension. Eur Respir J. 2013;41:523–538.

26. Sviryaev YuV, Kitalaeva KT, Korostovtseva LS et al. Treatment of hypertension associated with obstructive sleep apnea syndrome: rihnenidine vs. bisoprolol. Arterialnaya Gipertenziya = Arterial Hypertension. 2007;13(4):280–286. [In Russian].