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Selection of antihypertensive drugs from the perspective of clinical pharmacology

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Abstract

Background: The rational use of medicines remains one of the most important directions of public health, especially in socio-medical diseases, including arterial hypertension.
Material and methods: The study involved 28 cardiologists and 84 internists who, based on a set of questionnaires, expressed their opinion on ambulatory treatment of patients with arterial hypertension. Also 21 internists, 6 cardiologists and 6 obstetrician-gynecologists expressed their opinion on treatment of pregnancy-induced hypertension.
Results: Cardiologists and internists recommended angiotensin-converting-enzyme inhibitors (ACE inhibitors) in 28% of cases, diuretics – in 23% of cases, beta-blockers (BB) – in 20, 4% of cases, calcium channel blockers (CCB) – in 13.7% of cases, angiotensin receptor blockers (ARB) – in 13.6% of cases for ambulatory treatment of patients with arterial hypertension. The antihypertensive drugs from other pharmacological groups (with central action, alpha-blockers, arteriodilators, sympatholytics, etc.) were prescribed in only 1.3% of patients. On treatment of hypertension in pregnancy showed that all physicians – 100% recommended as first-line agent for treatment of hypertension during pregnancy centrally acting antihypertensive drug Methyldopa. For second-line treatment they recommended CCB – in 36.36% of cases, alpha-adrenoblockers – in 24.24% of cases, BB – in 21.21% of cases, diuretics – in 12.12% of cases and 3% for ACE inhibitors and ARB. For treatment pre-eclampsia and eclampsia seizures in 84.85% of cases is recommended Magnesium sulfate and 15.15% mention labetalol, hydralazine and sodium nitroprusside.
Conclusions: ACE inhibitors, diuretics, BAB, CCB and ARB have been first-line drugs in the arterial hypertension (AHT) treatment. For treatment of pregnancy-induced hypertension physicians recommended centrally acting antihypertensive drug Methyldopa. For second-line treatment they recommended calcium channel blockers (CCB), alpha-adrenoblockers, beta-blockers (BB) and diuretics. As third-choice in treatment of severe hypertension in preeclampsia are selected direct vasodilators as hydralazine, labetalol, sodium nitroprusside, and the most widely used in preeclampsia and eclampsia remains magnesium sulfate.

Key words: arterial hypertension, antihypertensive drugs, angiotensin-converting-enzyme inhibitors

Introduction

The rational use of medicines remains one of the most important directions of public health, especially in socio-medical diseases, including arterial hypertension (AHT). Hypertensive disorders complicate 5-10% of the pregnant and still now remain a leading cause of maternal mortality. The medicine data based on available and currently known evidences in the field of clinical pharmacology allow determination of the principles of selection and assessment of the use of medicines in the above-named diseases, which allow not only the optimization of rational use but also the reduction of the necessary expenditures and the increase of the harmlessness of the treatment [3, 4, 16, 19].

The aim of the study was to perform a pharmaco-therapeutic analysis compared with the elucidation of the groups of drugs and antihypertensive medicines used in the treatment of patients with hypertension and treatment of hypertension during pregnancy [2,3,4,5,8,10,18].

Material and methods

A survey study was conducted out by physicians from the medical institutions of Chisinau municipality in order to assess the incidence of prescribing different groups of antihypertensive drugs in the period October, 2015 – November, 2017. The study involved 28 cardiologists and 84 internists who, based on a set of questionnaires, expressed their opinion on ambulatory treatment of patients with arterial hypertension to determine the following aspects: frequency of use of the main groups of antihypertensive drugs and their representatives in patients with hypertension; correspondence of the pharmacotherapy stage and the degree of hypertension; the share of fixed combinations drugs for complex pharmacotherapy of arterial hypertension. Also 21 internists, 6 cardiologists and 6 obstetrician-gynecologists expressed their opinion on treatment of pregnancy-induced hypertension to determine the frequency of use of main groups of antihypertensive drugs.

Results

The results of the carried out study showed that cardiologists and internists recommended angiotensin-converting-enzyme inhibitors (ACE inhibitors) in 28% of cases, diuretics – in 23% of cases, beta-blockers (BB) – in 20.4% of cases, calcium channel blockers (CCB) – in 13.7% of cases,

angiotensin receptor blockers (ARB) – in 13.6% of cases for ambulatory treatment of patients with hypertension. The hypotensive drugs from other pharmacological groups (with central action, alpha-blockers, arteriodilator, sympatholytics, etc.) were prescribed in only 1.3% of patients. The reported data are in accordance with the national and international guidelines recommendations and reflect the contemporary strategy of approaching the hypertensive patient in terms of the initial and final goal of antihypertensive therapy [2, 3, 4, 5]. The analysis of literature data reveals that ACE inhibitors, ARB, BAB, CCB and diuretics are considered first-line antihypertensive drugs in the AHT treatment, and alpha-adrenoblocks, central-acting drugs, vasodilators and renin inhibitors are part of second-line antihypertensive medicines [3, 4, 15, 28, 31, 33].

The analysis of the drugs prescription from each pharmacological group was relevant to the fact that doctors recommended a wide range of representatives, selection being based on the particularities of drug release (free or compensated), age aspects, associated diseases, and target organ damage. Among the ACE inhibitors, doctors mentioned in the questionnaires almost all medicines registered in the Republic of Moldova.

Thus, the most frequent drugs in this group were ramipril (28.9%) and lisinopril (28.5%), followed by captopril (18.9%), enalapril (18.2%) and perindopril (4.9%). The angiotensin-converting-enzyme inhibitors, as first-line drugs in the AHT treatment, have an overwhelming evidence base in numerous trials and clinical guidelines, including patients with associated diseases such as diabetes mellitus, ischemic heart disease, cardiac failure, cardiac arrhythmias, atherosclerosis, renal diseases [2, 3, 4, 6, 15, 22, 26].

The ACE inhibitors pharmacodynamic profile is quite varied in terms of blood levels changes of angiotensin-converting-enzyme, angiotensin I, angiotensin II, renin, aldosterone and haemodynamic parameters, and also by organoprotective properties. The mechanism of action particularities determine the decrease of angiotensin II levels by blocking the respective more significant enzyme in organs and tissues than in plasma, especially in long-term treatment. Concurrently, ACE inhibitors also inhibit kinase II by increasing bradykinin content by stimulating the release of nitrogen monoxide and vasodilator prostaglandins.

The hypotensive action of ACE inhibitors is also due to other mechanisms: sympathetic tone activity reduction (decrease in adrenaline and noradrenaline level); aldosterone secretion decrease (natriuretic effect); endothelin secretion suppression; endothelial dysfunction amelioration.

Hemodynamic (reduction of peripheral vascular resistance, post- and preload, increased renal flow, etc.) and cardiac effects (regression of left ventricular hypertrophy, increase of coronary flow, reduction of postinfarction mortality, improvement of cardiac insufficiency, decrease of nitrate tolerance) are responsible for diminishing the myocardial remodeling progression and vascular smooth muscle hypertrophy to prevent damage to organs and systems which reflect beneficially on the quality of life, morbidity and mortality of patients with cardiovascular diseases [3, 4, 6, 15, 16, 24, 26, 28].

Diuretics, as expected, occupied the second position in doctors' preferences. Indapamide (35.7%), spironolactone (26.8%), furosemide (16.5%), torasemide (12.7%) and hydrochlorothiazide (8.3%) were among the diuretics recommended to the patients. The use of diuretics in the HTA treatment is determined by the drugs ability to reduce blood pressure and to remove refractory mechanisms in other hypotensive groups. The antihypertensive action of diuretics is determined by various mechanisms depending on the duration of use. Thus, blood pressure lowering is achieved by the moderate effect of natriuresis with the reduction of circulating blood volume and preload, respectively, at the initiation of treatment (the first 4-6 weeks). The circulating blood volume is restored in long-term use and blood pressure lowering is possibly achieved by reducing vascular tone through several mechanisms: synthesis of vasodilator prostaglandins (indapamide, furosemide, torasemide); blockage of calcium channels (indapamide); activation of potassium channels (indapamide); reducing vascular intimal infiltration with sodium ions [3, 4, 20, 31, 33].

The quite frequent use of indapamide, a third generation non-thiazide diuretic, is argued by pharmacodynamic peculiarities, good tolerability and harmlessness, a salutary preparation in the long-term treatment of AHT. Indapamide, in addition to the hypotensive effect particularities, is characterized by beneficial influences on thiazides, on glucose metabolism (it does not produce hyperglycemia, does not disturb the sensitivity of peripheral tissues to insulin), lipid (a minimal effect on cholesterol level, triglycerides, increases the content of high density lipoproteins), electrolytic (practically does not produce hypokalaemia) and purine (does not increase uric acid level) [20, 31, 33].

The elucidation of new pathogenetic aspects of AHT, including refractoriness in the first-line drugs, has demonstrated the role of aldosterone in cardiovascular pathology through genomic and non-genomic mechanisms. Thus, the "aldosterone rickets" phenomenon was described, which occurs in AHT patients treated with inhibitors of the renin-angiotensin-aldosterone system due to incomplete inhibition of mineralocorticoid activity. The use of antagonist competitors of aldosterone (spironolactone, eplerenone), considered to be the second, third or even the forth-line drugs, under these conditions, contributed to the increase of efficacy and removing refractoriness in antihypertensive drugs [27, 30].

Spironolactone, a non-competitive antagonist of aldosterone, contributed to prevent progression of target organ damage and the development of complications, loss of potassium and magnesium ions. However, the high adverse reactions incidence (breast tightening, gynecomastia, erectile dysfunction, amenorrhea, hirsutism, etc.), determined by the steroid structure and influence on androgen receptors, limits patients' compliance with the treatment.

In this context, a particular interest is given to eplerenone, a selective antagonist of aldosterone, a product that is characterized by better tolerability and harmlessness. At the same time, it is estimated that, if spironolactone predominantly influences the mineralocorticoid genomic mechanisms, eplerenone is able to annihilate non-genomic ones, thus exhibiting a faster effect [1, 20, 27, 30, 31, 33].

The lower incidence of loop diuretics use is explicable because these drugs are prescribed by doctors in emergency situations, in severe AHT and associated with complications; in case of the renal function alteration (2^{nd}-3^{rd} degree). The rather high frequency of torasemide prescription due to its advantages over furosemide (effect up to 24 hours, less incidence of side effects, including the severe ones, better treatment compliance in patients) is significant [20, 31, 33].

Hydrochlorothiazide, although had the lowest use incidence, remains a thiazide in demand, especially in the forms combined with ACE inhibitors, ARB, BB, CCB, due to the moderate and constant antihypertensive effect, the ability to decrease the counterregulatory mechanisms in the case of refractoriness to other hypotensives, despite characteristic metabolic reactions [17, 20, 31, 33].

Beta-blockers were recommended relatively quite frequently (20.4%), which corresponds to the literature data [7, 8, 11, 19, 24]. Bisoprolol (45.7%), followed by metoprolol (29.2%), nebivolol (8.1%), and atenolol (7.7%) were most frequently prescribed drugs from this group. Carvedilol and propranolol were recommended with lower incidence. The relatively high incidence of BB in hypertensive patients is determined by an increase in the number of drugs of this group, especially cardioselective ones (bisoprolol, atenolol, metoprolol, acebutolol, etc.) and with vasodilatory action (nebivolol, carvedilol). The antihypertensive effect of BB is determined by several mechanisms: heart rate decrease; decrease of renin secretion and renin-angiotensin-aldosterone system activity; modification of the aorta baroreceptors sensitivity and sino-carotid glomerus; reduction of sympathetic central genesis; dilation of vessels by nitrogen monoxide production, alpha-adrenoreceptors blockade or direct myotropic action [3, 4, 7, 8, 29].

Among the CCB, the largest share goes to the dihydropyridine derivatives (73.1%), followed by the benzothiazepine derivatives (13.4%) and phenylalkylamine derivatives (10.7%). Dihydropyridines were represented by amlodipine (61.8%) and nifidipine (11.3%), and by lercanidipine, lacidipine, etc. in a smaller percentage.

Among the CCB with concomitant action on vessels and heart, diltiazem was prescribed in 13.4% of cases and verapamil in 10.7% of cases. The more frequent use of amlodipine is argued by pharmacological peculiarities: high bioavailability due to lipophilic properties; rapid onset of action; absence of neuroendocrine and sympathetic reflex mechanisms on heart and metabolism; the long half-life that determines convenience in administration (once a day) and patient's good compliance with the treatment; a lower incidence of side effects; increase in nitrogen monoxide production; the antioxidant properties presence.

These priorities determine the use of amlodipine as a first-line antihypertensive drug as a monotherapy and an important component in combined therapy with almost all hypotensive groups including patients with comorbidities (angina pectoris, atherosclerosis, diabetes mellitus, kidney disease) [3, 4, 11, 14, 23].

On the basis of randomized studies and meta-analysis, it was determined that CCB does not cede to ARB, ACE inhibitors, BAB, diuretics and alpha-adrenoblockers in blood pressure control, risk of cardiovascular (death, myocardial infarction, heart failure) and cerebrovascular events [14, 24].

Doctors recommended ARB with a similar incidence of CCB – 13,6%. Losartan (61.8%) and valsartan (33.2%) predominate among the drugs of this group. It is necessary to mention that in the doctors' preferences there were also mentioned such ARB as irbesartan (2.5%), telmisartan (1.25%), and candesartan (1.25%), drugs with some more advantageous pharmacological features welcomed in certain clinical situations. Angiotensin receptor blockers in European countries are prescribed to 20-25% of AHT patients because they are considered as the basic pathogenetic therapy that allows safe and adequate blood pressure control, prevention of target organ damage and complications. The use of ARB provides for a more complete blockade of the renin-angiotensin-aldosterone system because it blocks the action of angiotensin II on specific (type 1) receptors produced not only by angiotensin converting enzyme but also by alternative routes (chymase, etc.). At the same time, angiotensin II activity is maintained on 2nd type of angiotensin receptors while maintaining physiological effects (vasodilation, antiproliferative action, etc.). Concomitantly, metabolism of bradykinin, encephalins and other biologically active peptides, responsible for some specific side effects of ACE inhibitors that activate the quinine system, is not affected. The drugs of this group are characterized by a stable antihypertensive effect over 24 hours with a stable clinical effect after 3-4 weeks. Sartans exhibit favorable metabolic actions on lipid and carbohydrate metabolism, beneficial effects in patients with diabetes mellitus, dyslipidemias, metabolic syndrome, atherosclerosis of vessels. Clinical studies have shown decrease of glucose and insulin resistance level (stimulation of PPAR- nuclear receptors in adipose and muscle tissue, hepatocytes). It was proved the ARB capacity to reduce the contents of triglyceride and low density lipoprotein cholesterol. These effects, along with the improvement of endothelial dysfunction, will be welcomed in patients with the mentioned pathologies [3, 4, 6, 16, 22, 25, 26, 32].

Among the hypotensive preparations in other groups, the doctors have opted for centrally acting anti-hypertensives and alpha-1-adrenoblocking agents. It is necessary to mention that the imidazoline receptor agonist, moxonidine (52.5%), predominates among the medically active drugs compared to the methyldopa (20%) and clonidine (17.5%)

alpha-2 adrenomimetics. Among the selective alpha-adrenergic blockers, doxazosin was recommended in 10% of cases.

The therapeutic behaviour according to the degree of arterial hypertension was another aspect of the pharmacoepidemiological study. Thus, the investigations analysis revealed that doctors preferred monotherapy (86.4%), and the association of 2 drugs in 12.8% and association of 3 drugs only in 0.8%, in case of hypertension of the first degree.

In patients with arterial hypertension of second degree, the doctors mentioned the need for prescribing 2 drugs (65.5%), while monotherapy was sufficient in 21.2%, and triple therapy was required in 13.3% of patients. For hypertension of third degree, treatment with 3 hypotensive drugs (46.6%) is recommended. At the same time, doctors mentioned that about 38.7% of the patients responded adequately to treatment with 2 antihypertensives, and even 4 hypotensive preparations were recommended in 14.7% of patients. These data fully reveal the actual clinical situation due to target organ damage with the progression of high blood pressure.

The survey showed that doctors preferred associations between one drug from different groups (64.4%) in case of combined antihypertensive drug therapy, while fixed-dose combinations were recommended in only 26.7% of cases. The association of one drug with fixed-dose drugs combinations was used in 8.9% of cases.

The results on treatment of hypertension in pregnancy showed that all physicians -100% (21 internists, 6 cardiologists and 6 obstetrician-gynecologists) recommended as first-line agent for treatment of pregnancy-induced hypertension, centrally acting antihypertensive drug methyldopa. Accordingly to literature data methyldopa is one of the most widely used drugs for the treatment of hypertension during pregnancy (Category B, safe, accordingly to Food and Drugs Administration, FDA, USA classification of drugs in pregnancy). It is a prodrug metabolized to alpha methylnorepinephrine, which then replaces norepinephrine in the neurosecretory vesicles of adrenergic nerve terminals. Methyldopa inhibits vasoconstriction via a central mechanism by reducing catecholamine release [3, 4, 18]. It decreases central sympathetic outflow, decreasing systemic vascular resistance, without decreasing cardiac output BP control is gradual, over six to eight hours, because of the indirect mechanism of action. Treatment with methyldopa has been reported to prevent subsequent progression to severe hypertension in pregnancy and does not seem to have adverse effects on utero-placental or fetal hemodynamics. Adverse effects are based on pharmacodynamics effects – central alpha-2 blocking effect or decreased peripheral sympathetic tone. This drug can cause decreased mental alertness and impaired sleep, leading to sense of fatigue in some or depression in others. Still other observed side effects are decreased salivation, leading to xerostomia (chronic dry mouth), elevated liver enzymes in 5%; hepatitis and hepatic necrosis have been reported. Some patients will develop a positive antinuclear antigen or antiglobulin (Coombs') test with chronic use, which may occasionally cause clinical hemolytic anemia. However, it is not considered to be teratogenic based on limited clinical study data and forty-year clinical experience [3, 4, 8, 18]. Another central acting agent is clonidine (Category C, less safe, accordingly to FDA classification of drugs in pregnancy), a selective alpha-2 agonist, acts similarly and is comparable to methyldopa with respect to efficacy, but regarding to some safety concern there is a small controlled follow-up study with neonates that reported an excess of sleep disturbance in clonidine-exposed infants. So, in pregnancy, it is recommended to be used as a third-line agent for multidrug control of refractory hypertension [10, 18].

For second-line treatment our doctors recommended calcium channel blockers (CCB) – in 36.36% of cases, alpha-adrenoblockers – in 24.24% of cases, beta-blockers (BB) – in 21.214% of cases, diuretics – in 12.12% of cases and 3% for angiotensin-converting-enzyme inhibitors (ACE inhibitors) and angiotensin receptor blockers (ARB).

Calcium channel blockers have been used to treat chronic hypertension, mild pre-eclampsia presenting late in gestation and urgent hypertension associated with pre-eclampsia (Category C, less safe, accordingly to FDA classification of drugs in pregnancy, but amlodipine is classified as Category D-Teratogenicity in animals). Both nifedipine and verapamil are not associated with teratogenic risks to fetus exposed in first trimester. Maternal adverse effects with nifedipine include pharmacodinamic type as tachycardia, palpitations, peripheral edema, headaches, and facial flushing. Nifedipine does not seem to cause a detectable decrease in uterine blood flow. Short-acting dihydropyridine calcium antagonists sublingually are associated with maternal hypotension and fetal distress and are generally not recommended. In contrast long-acting oral nifedipine in pregnant patients with severe hypertension during pregnancy has been shown to be safe and effective. Dihydropyridine compounds: I-generation (nifedipine); II generation (felodipine, isradipine, nicardipina) also have a tocolytic effect and can delay the onset or slow the progression of labor. Phenylalkylamine agent as verapamil and benzothiazepine class as diltiazem may have additional value in women with proteinuria because of their antiproteinuric action [3, 4, 10, 18].

Both groups alpha-adrenoblockers and beta-blockers (BB) are recommended by our doctors with the same frequency (pindolol and acebutolol are classified as Category B, but atenolol, propronalol, metoprolol, timolol and labetalol – Categoty C). Accordingly to Cochrane analysis, beta-blockers were found to be more effective in lowering blood pressure than methyldopa. Labetalol, a nonselective alpha-and beta-blocker has obtained wide acceptance to treat sever hypertension in pregnancy, because of lower incidence of side effects in comparison with hydralazine- direct vasodilator Category C, associated with more maternal and perinatal adverse events, than other agents when used acutely [10,18].

Diuretics were recommended in 12.12% of cases, hydrochlorthiazide (Category B, safe), accordingly to FDA classification of drugs in pregnancy). Administration of diuretics in pregnancy remains a matter of dispute because of fluid and electolytes disturbances. The potassium sparing diuretics spironolactone, triamterene and amilorid are not recommended in pregnancy – Category D (teratogenicity in animals, accordingly to FDA classification of drugs in pregnancy).

Angiotensin-converting-enzyme inhibitors (ACE inhibitors) and angiotensin receptor blockers (ARB) were recommended in 3% of cases. These groups of antihypertensive agents that are used as first-line choice in treatment of essential hypertension are contraindicated in pregnancy because of severe toxicity secondary to reduced renal perfusion of the fetal kidneys (Category D, teratogenicity in animals, accordingly to FDA classification of drugs in pregnancy). Their use has been associated with renal dysgenesis, oligohydramnios as consequence of fetal oliguria, pulmonary hypoplasia, intrauterine growth restriction, and neonatal anuric renal failure, leading to death of the fetus. ARBs have also been associated with fetal demise and same concerns are applicable to the use of direct renin inhibitors. First trimester exposure to these agents has been associated with greater incidence of cardiovascular and central nervous system malformations. Whether these effects are secondary to hemodynamic effects or specific requirement of angiotensin II as a fetal growth factor is unknown. Patients should, therefore, be counseled to stop these medications while attempting to conceive. The risk of birth defects increased from 3 to 7% while on these medications at the time of conception [8, 10, 12, 13,18].

For treatment pre-eclampsia and eclampsia seizures in 84.85% of cases doctors recommended magnesium sulfate (Category A, most safe, accordingly to FDA classification of drugs in pregnancy).

Conclusions

On the basis of carried out study, it was found that ACE inhibitors, diuretics, BAB, CCB and ARB have been first-line drugs in the AHT treatment. The drugs selection was performed on the basis of national and international guidelines and the pharmacological properties of the antihypertensive drug groups. The use of second-line antihypertensive drugs (central-acting alpha-2-adrenomimetics, imidazolinone derivatives, alpha-1 adrenoblockers) denotes that the choice of antihypertensive therapy also takes into account the particularities of AHT evolution in the patient, especially in detected associated diseases and metabolic disturbances.

Based on the results obtained from the questionnaire on the treatment of pregnancy-induced hypertension, it was demonstrated that first-line agents remain central acting agent, alpha 2 adrenoreceptor agonist like methyldopa, which is in conformity with national and international protocols and guidelines. As second-line choice in the treatment of pregnancy-induced hypertension we can mention calcium channel blockers (CCB), alpha-adrenoblockers, beta-blockers and diuretics. As third-choice in treatment of sever hypertension in preeclampsia are selected direct vasodilators as hydralazine, labetalol, sodium nitroprusside and the most widely used in preeclampsia and eclampsia remains magnesium sulfate. It is very important to note that angiotensin-converting-enzyme inhibitors (ACE inhibitors) and angiotensin receptor blockers are contraindicated in pregnancy and must not be recommended for pregnancy-induced hypertension.

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