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Research Article

Pharmacological Effects of Antihypertensive Drugs in Elderly Patients

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ABSTRACT.

Introduction. The incidence of arterial hypertension (AH) increases. Only 23% of Russian patients monitor their blood pressure. This affects the incidence of complications, the quality and duration of life. The largest number of deaths related to the irrational pharmacotherapy of hypertension occurs in the older age group.

Methods. We have carried out a review of publications in scientific and medical literature, the analysis of the current state of views on the incidence, pathogenesis, and peculiarities of the treatment of hypertension in elderly patients.

Results. An isolated systolic arterial hypertension (ISAH), typical of the elderly people, is associated with a reduction in the elasticity of the arterial walls. The reaction of the elderly to the medicines is largely determined by the severity of age-related changes. We have considered four factors influencing the effect of drugs such as absorption, distribution, metabolism and excretion of drugs.

Discussion. Treatment in elderly patients is aimed at reducing the symptoms and compensating the disturbed functions. It is necessary to be able to detect that symptoms in the structure that affect quality of life and require therapeutic intervention. Physiological aging processes lead to changes in the pharmacokinetics and pharmacodynamics of drugs. The therapeutic effect is affected by changes in absorption, distribution volume, metabolism and excretion of drugs. In this connection there is an increased amount of drug in the bloodstream.

Final Report. Knowing the geriatric aspects of cardiology is an important element of knowledge of a modern doctor.

Keywords: arterial hypertension, antihypertensive therapy, pharmacological effects, old age.

INTRODUCTION.

There are more than 700 million people over 60 years old in the world. By 2025, their number will reach 1.1 billion [1]. According to the new WHO classification, 25-44 years old - a young age, 44-60 years old - an average age, 60-75 years old - a prehensile age, 75-90 years old - senile age, and over 90 - centenarians [2]. Decrease in the adaptive capabilities of the organism, changes in its reactivity create conditions for the pathologic development [3]. The incidence rate in the elderly is almost two times higher, and in the senile people - 6 times

higher than in young people. On average, one patient over 60 years old has 4-5 different diseases detected [5]. One of the most common diseases of the elderly people is an arterial hypertension (AH) [6]. Its incidence among people over 65 years old increased twice in the last 40 years, and in people over 80 years the incidence rate of hypertension exceeds 60% and continues to grow [7]. Only 23% of Russian patients monitor their blood pressure (while in USA and Canada the BP is monitored by nearly 50% of people). This affects the incidence of complications, the quality and duration of life. The presence of comorbidities increases the intake of drugs by elderly patients, which increases the probability of drug interactions. The risk of side effects in patients older than 60 years increases by 2-3 times, as compared with young people [10]. This is due to changes in the pharmacokinetics and pharmacodynamics of drugs in the elderly body [11]. Knowing the age-related aspects of cardiology is an important element of knowledge for geriatricians, cardiologists, family doctors and general practitioners [9, 12, 13].

METHODS.

We have conducted the analysis of recent publications devoted to the peculiarities of arterial hypertension development in older patients, and age-related changes in pharmacokinetics and pharmacodynamics of this group of patients.

RESULTS.

Old age is characterized by the following changes in the heart and blood vessels: fibrosis and hypertrophy of the left ventricle (LVH) with increased rigidity of its myocardium and impaired filling of the left ventricle; in myocardiocytes: enhanced apoptosis and autophagy, decreased number of myocardiocytes, changes in myosin isoforms, impaired regulation and function of calcium channels, prolongation of membrane action potential, decelerated contractility; changes in the autonomic nervous system, reduced number and function of adrenergic receptors in the myocardiocytes; decreased response of the heart rate (HR) to exercise (heart rate reserve) with a decrease in load endurance; reduced number of pacemaker cells of the sinus node, fibrotic changes in the structures of the vascular system; calcification and fibrosis of the heart valves; induration and stiffening of the artery walls, increased pulse wave distribution rate, decreased bar reflex sensitivity; reduced formation of vasodilatory substances by the vascular endothelium; increased level of procoagulative and proinflammatory cytokines, and increased oxidative stress. All of the above causes the main features of arterial hypertension in the elderly [14, 15]. An isolated systolic arterial hypertension (ISAH) associated with a decrease in artery wall compliance (80-90%) is typical of the elderly patients [16]. ISAH is characterized by the increased systolic blood pressure (SBP) and decreased diastolic blood pressure (DBP). Increased SBP is a factor of the development of left ventricular hypertrophy, and decreased diastolic blood pressure leads to deterioration of cerebral and coronary blood flow. The ISAH incidence increases with age and is 0.1% among those under 40 years old, 0.8% of those aged 40-49, 5% of those aged 50-59, 12.6% - 60-69 years old, and 23.6% of those aged 70-80 years. This is attributed to the fact that the increase in SBP occurs at least until the age of 80 years, while the DBP after 50 years old either remains at the same level or tends to decrease [9]. ISAH in elderly people is associated with a significant increase in cardiovascular risk at comparable SBP values. Low levels of DBP (60-70 mm Hg and lower) are associated with an additional increase in the risk [17].

"White-coat hypertension" ("office hypertension") can be diagnosed when blood pressure, measured in a doctor's office, is ≥ 140/90 mm Hg at least in 3 cases at normal values of blood pressure at home and according to the daily monitoring of blood pressure. This variant of hypertension is more commonly observed in the elderly and in women. Cardiovascular risk in these patients is lower than in patients with common hypertension, but probably higher than in normotensive individuals [18-20]. Patients over 60 years old can have hypertension with frequent short-term,

paucisymptomatic blood pressure rises to high values, which alternate with a drop in blood pressure below normal values. Such episodes may occur for no apparent reason, or as a result of taking low doses of antihypertensive drugs. In the pathogenesis, the autonomic disorders make a difference [9]. Physiological aging processes lead to changes in the pharmacokinetics and pharmacodynamics of drugs [1, 9, 21]. They are accompanied by a decrease in the suction surface of the digestive tract, reduced secretory activity, weakening GI motility and decelerated evacuation, and the decreased blood flow in the mesenteric vessels. Changes in the gastric pH may interfere with the dissolubility and ionization of drugs in the stomach and their pH-dependent absorption. Achlorhydria can cause an increased absorption of unstable drugs. The weakening of the gastrointestinal tract motility and slowing of the evacuation capacity slows down the absorption of drugs and increases the development time of therapeutic effect. At the same time, the absorption of drugs increases due to prolonged stay of drugs in the gastrointestinal tract. In combination with the elimination deceleration, it requires dose reduction and correction of the prescription mode. In case of intramuscular administration, the absorption of drugs in the blood also slows down due to the decelerated blood flow and changes in the permeability of the vessel walls. Transdermal absorption of drugs is also impaired due to skin aging, atrophy and degenerative processes. The number of vessels and the permeability of their walls also decreases. Microcirculation disorders are manifested in the form of stasis, microthromboses, capillary dropout [1, 12].

“Distribution volume” (DV) is a hypothetical volume of liquid, in which the drug can be distributed at a concentration equal to its concentration in plasma. In young individuals, this index is about 30 liters, whereas in older age it decreases up to 20. With aging, both degree and rate of drug distribution can be disturbed as a result of reduction of the cell mass, as a result of the reducing body weight, changes in its composition and because of circulatory disorders. Changes in DV also occur due to the replacement of metabolically active tissues with fat tissue, reduction in the total amount of water in the body, and changes in tissue permeability. Reduced muscle mass and amount of water leads to the reduced DV of hydrophilic drugs and their increased concentrations in plasma and tissues. An increasing amount of adipose tissue in older age increases DV and reduces the concentration of lipophilic drugs in the tissues, which is accompanied by deceleration of the beginning and increased duration of their action.

The distribution of drugs is also determined by their binding to proteins, since only an unbound drug can diffuse into the tissue or be excreted. Aging is accompanied by a decrease in albumin content in plasma by 10-15%. Hypoalbuminemia reduces the bound drug fraction and increases concentration of its free fraction, which increases the possibility of overdose. This has implications for drugs with a high plasma proteins binding ability (80%). An increased concentrations of drug-binding α_1-acid glycoprotein is also observed in the elderly, which can slow the pharmacological action. The distribution of medicines is influenced by such circulatory disorders as a decrease in cardiac output (by about 1% per year), deceleration and redistribution of blood flow, changes in tissue permeability. With aging, the sympathetic tone increases, which negatively affects renal and hepatic blood flow and leads to a decrease in the metabolic clearance of drugs [1, 10].

The elderly patients often have a decelerated drug metabolism due to atrophy of the hepatic parenchyma, reduced number of hepatocytes, decreased activity of microsomal enzymes and metabolic disorders. The hepatic mass in patients over 65 years old is reduced by 25%, and the hepatic blood flow - by approximately 40%, which leads to increased bioavailability of drugs and increase in their plasma concentration. Phase I of the hepatic metabolism (oxidation, hydrolysis) performed by the system of microsomal cytochrome P_{450} enzymes is more significantly disturbed, whereas the phase II reactions (synthetic reactions) are significantly less impaired. In case of withdrawal of metabolism-accelerating drugs, anticoagulant doses must be reduced in order to prevent bleeding complications. Also, there is an

observed increase in bioavailability of drugs with high "first pass effect" caused by their reduction. A reduced metabolic function of the liver also contributes to the accumulation of metabolic products of drugs in the body, which facilitates the development of drug-induced intoxication.

Renal excretion is the major way of elimination for most drugs. With aging, the renal function is reduced even in the absence of discernible diseases. The elderly have decelerated drug excretion by the kidneys due to the preferential atrophy of the cortical layer, reduced number of functioning glomeruli, decreased renal blood flow rate and glomerular filtration rate (GFR), and histological changes in the tubules. Sclerosis of renal arterioles leads to a decrease in GFR by nearly 1% per year after 50 years old, which leads in the elderly people to moderate kidney failure. However, serum creatinine is not increased because its production is reduced proportionally to the reduction of muscle mass with aging. In parallel with reduction in GFR, there is a partial loss of tubular secretion and reabsorption. Reduced renal function leads to increased concentrations of drugs being excreted unchanged or as active metabolites, and increases their half-life period, creating a risk of drug accumulation. Influence of drugs on the body in old age has its particular features. Worsened drug delivery to the tissues is combined with a reduction in the number of receptors to drugs, but patients' sensitivity to the drug at the same time may increase and even be perverted. This explains an diverse response of a senile organism to drugs and the difficulty of its prediction. Such effect can be promoted by a reduce physical activity, lower consumption of food and water, a tendency to constipation, vitamin deficiency, deterioration of blood supply to the tissues and the relative predominance of excitatory processes of the nervous system in the elderly people. Changes in the cardiovascular system increase the sensitivity of the elderly people to vasodilators, antihypertensive and diuretics [22-24]. The set of the considered features leads to a significant increase in the risk of adverse reactions caused by antihypertensive drugs in elderly patients, especially at their combined intake [25].

SUMMARY.

Physiological aging processes lead to changes in the pharmacokinetics and pharmacodynamics of drugs. The therapeutic effect is affected by changes in absorption, distribution volume, metabolism and excretion of drugs. Knowing the geriatric aspects of cardiology is an important element of knowledge of a modern doctor.

CONCLUSION.

Knowing the geriatric aspects of cardiology is an important element of knowledge of a modern doctor.

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