Review

Age peculiarities of pharmacokinetics and pharmacodynamics of medicines

L.P. Kuprash¹, S.A. Gudarenko¹, O.V. Kuprash¹, N. A. Gorchakova², O.V. Khodakivska²

¹State Institution "D. F. Chebotarev Institute of Gerontology NAMS of Ukraine", Kyiv, Ukraine

²The Bogomolets National Medical University, Kyiv, Ukraine

Correspondence: kuprash@geront.kiev.ua

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Abstract. The drug therapy of elderly and senile patients is characterized by a number of features due to morphological, metabolic and functional disorders that occur in the body during aging at all levels of the body's life activity: the molecular genetic level, cellular level, the organ level, the regulatory level. As a result, the drugs' pharmacokinetics and pharmacodynamics of drugs change which has a significant impact on the effectiveness and safety of drug therapy in elderly and senile patients

Keywords: Drug therapy, pharmacokinetics of medicines, pharmacodynamics of medicines, aging.

With age, the main elements of drug pharmacokinetics - absorption, distribution, biotransformation and elimination - change significantly [1, 2, 3, 4].

As a result of structural and functional changes in the digestive system during aging, the absorption of drugs prescribed internally is disrupted [5, 6].

The absorption in the gastrointestinal tract during aging is characterized by a decrease of the suction surface, reduced motility, delayed evacuation, decreased secretory activity, and decreased blood flow in mesenteric vessels, which leads to slower absorption [5]. The weakening of intestinal motility and slowing down the evacuation capacity of the stomach in elderly people are very important [3]. Therefore, a number of drugs enter the body of elderly people in a slightly smaller amount and more slowly than in young patients [7].

As a result of reducing the amount of gastric juice in old people, the absorption of drugs in the stomach that are chemically acids - salicylates, barbiturates, nitrofurans, anticoagulants and some sulfonamides - decreases. It not only slows down their entry into the blood and reduces the therapeutic effect, but also as a result of a longer stay in the stomach, causes an irritating effect on its mucous membrane, which is accompanied by dyspeptic phenomena and pain in the epigastric region, and it can also lead to the formation of ulcers in the stomach, gastric bleeding [8, 9].

In the aging process the volume of distribution of drugs decreases due to decrease in the pumping function of the heart, impaired tissue microcirculation, reduction of water spaces of the body, the fat depot [3, 10].

The reduction of water spaces leads to the decrease in the volume of hydrophilic drugs distribution and the increase in their concentration in blood plasma and tissues, which increases the risk of overdose and drug intoxication. It refers to aminoglycoside antibiotics, cardiac glycosides, beta-blockers, and calcium channel blockers [11].

The increase in the amount of adipose tissue in the older age contributes the increased volume of distribution and decreased concentrations of lipophilic drugs in tissues, which is accompanied by a

slower start and longer duration of action. It refers to tetracyclines, benzodiazepine tranquilizers, phenothiazine neuroleptics, and barbiturates [11].

The important aspect of the distribution of the drug in the body is its binding to plasma proteins, since only an unbound drug can diffuse into the tissue or be excreted from the body. The aging of the body is accompanied by the decrease in the content of albumins in the blood plasma by an average of 10-15%. Hypoalbuminemia leads to the decrease in the bound fraction of the drug and the increase in the concentration of the free fraction which increases the effectiveness of the drug, as well as increases the possibility of overdose, toxic and adverse reactions. The concentration of many drugs in plasma in elderly patients increases significantly, sometimes reaching a toxic level, especially in drugs with a small therapeutic margin. It is especially important for drugs that have a high degree of binding to plasma proteins (more than 80%) - beta-blockers, sulfonamides, salicylates, cardiac glycosides, benzodiazepine tranquilizers, indirect anticoagulants, antidiabetic agents, narcotic analgesics, anticonvulsants [12, 13].

A significant role in age-related changes in the pharmacokinetics of drugs is the decrease of systems activity in the process of aging, these systems perform their biotransformation, primarily the decrease of the activity of microsomal liver enzymes- monooxygenase (cytochrome P450), aminopyrin-n-demethylase, and hexobarbital hydroxylase [14, 15].

When studying liver biopsies in patients older than 70 years, the content of cytochrome P450 was 32% lower than in patients aged 20-29 years, after 40 years the concentration decreased by an average of 0.07 nmol/g per year [16].

Along with it, the activity of the second phase of hepatic biotransformation of drugs – conjugation - decreases in old age [4].

Slowing down the metabolism of drugs with age contributes to a longer-term maintenance of their therapeutic concentrations in the tissues of the old body. First of all, it refers to drugs that are actively metabolized in the liver - neurotropic drugs, beta-blockers, cardiac glycosides, non-steroidal anti-inflammatory drugs, anticoagulants. Taking into account the age-related decrease in the induction of microsomal oxidation enzymes, special care is required to prescribe these groups of drugs to elderly and senile patients in association with medications of microsomal enzyme inducers which include barbiturates, tranquilizers, spironolactone, rifampicin, and others [7, 10, 17].

With age kidney function decreases, renal blood flow and glomerular filtration decreases which determines to a large extent the slowing of renal elimination of drugs in the senile body. The glomerular filtration rate measured by endogenous creatinine clearance is reduced by 35-50% in the elderly [18].

The decrease in renal function leads to the concentration increase of drugs that are excreted unchanged, and active or toxic metabolites, as well as increases the half-life, creating a risk of drug accumulation, overdose, and side effects [11].

Age-related changes of the main components of drug pharmacokinetics -absorption, distribution, biotransformation, and elimination - lead to the decrease in the clearance of most drugs in the elderly and senile age and the extension of their half-life [4, 7].

Therefore, it is necessary to correct doses of drugs for elderly patients with a small margin of therapeutic action: cardiac glycosides (strofantin, corglikon, digoxin), aminoglycoside antibiotics, as well as cephalosporins, antidiabetic, antiarrhythmic, diuretic agents, clonidine, non-steroidal anti-inflammatory drugs. Prescribing a standard adult dose to an elderly patient may lead to a disproportionately high serum content of the drug [19].

The level of the antibiotics concentration in the blood of older people is higher than in young people. The accumulation of antibiotics in the body leads to the development of undesirable reactions, whose number increases with age from 11.8% at the age of 40 to 45 years to 24% at the age of more than 80 years, so it is recommended to lengthen the intervals between their administration in patients of older age groups [20].

Along with age-related changes in pharmacokinetics, with aging the pharmacodynamics of different drug groups changes due to alterations in the number of farmacoreceptors, their sensitivity to drugs, as well as changes in the metabolites content, activity of enzymes, the reactions of the internal environment of the body, the reactivity of the nervous system [21, 22, 23, 24].

So, in the process of aging, the number of beta-adrenergic receptors in tissues decreases, their sensitivity to stimulating and blocking effects changes which causes the frequency of complications

(bradycardia, hypotension,) when prescribing this group of drugs to patients older than 60 years. The use of beta-blockers in patients of older age groups requires considerable caution [25, 26].

With age, the sensitivity of baroreceptors increases. Therefore, when calcium antagonists are prescribed to older patients, orthostatic hypotension may develop due to a sharp decrease in blood pressure which dictates the need to prescribe lower doses of the drug [27, 28].

With age the sensitivity to the action of anticoagulants increases. At the same time due to age-related hypoalbuminemia in old age, the fraction of drugs associated with albumins decreases and the concentration of the free fraction in the blood plasma increases which dictates the need to prescribe these drugs to patients of older age groups in smaller doses [29, 30, 31].

In case of the glycosidotherapy in elderly patients, complications are often observed due to the increase in the sensitivity of the old heart to the action of glycosides because of age-related metabolic changes in the myocardium (electrolyte composition, acid-base balance, activity of membrane-bound enzymes, in particular, transport ATPases which are considered specific receptors for cardiac glycosides on the plasma membrane of cardiomyocytes). Therefore, the administration of cardiac glycosides to elderly and senile patients requires special attention (the drug selection, the dose determination, the concomitant therapy) [32]. When taking diuretics, patients of older age groups lose more fluid than young ones, they have more pronounced hypokalemia, hypouricemia, hypovolemia, dehydration with azotemia. According to various authors, adverse reactions during diuretic therapy in older people are observed in 6-12% [33].

As a result of age-related changes of the central nervous system, disturbances in the processes of excitation and inhibition in old age, sensitivity to narcotic and hypnotic drugs is significantly increased [17].

In consequence of age-related changes in the dopaminergic system (the decrease in endogenous dopamine levels and the decrease in the density of dopamine receptors), sensitivity to antipsychotic agents increases with age [34, 35].

When prescribing tricyclic antidepressants for older patients, the anticholinergic, sedative, and cardiovascular side effects are often observed [36, 37].

Age-related changes in the pharmacokinetics and pharmacodynamics of drugs increase the risk of adverse reactions in elderly and senile patients which is particularly dangerous in conditions of age-related polypragmasia [11, 17]. Increasing the frequency and severity of chronic disease raises the level of polypragmasia, reaching more than 6-7 drugs per patient in patients of older age groups [38, 39, 40, 41].

The consequence of polypragmasia in older patients is the increase in the risk of adverse reactions as a result of drug interactions [42, 43]. The frequency and severity of adverse reactions in drug interactions correlates with age and the number of prescribed medications [44, 45].

Adverse reactions in the interaction of drugs develop both at the stage of transport and metabolism (pharmacokinetic interaction) and at the level of pharmacoreception (pharmacodynamic interaction). Among the adverse reactions registered in elderly patients with diseases of the circulatory system, 64.9% were developed due to pharmacokinetic interaction, 20.1% – due to pharmacodynamics one, and 15.0% of the mechanisms of drug interaction were not established [41].

Special attention in the treatment of elderly and senile patients must be paid to undesirable reactions that occur during pharmacokinetic interaction in the process of drug biotransformation. Due to the age-related decrease in the activity of cytochrome P450, the blood concentration of drugs actively metabolized by this enzyme increases significantly which is accompanied by the risk of adverse reactions, especially when inhibitors of this cytochrome are prescribed simultaneously [46].

Thus, the metabolism of the beta-blockers of metoprolol, propranolol, and carvedilol occurs with the participation of cytochrome P450. The prescription of these drugs simultaneously with enzyme inhibitors (amiodarone, cimetidine, antidepressants) to elderly patients increases the risk of bradycardia (less than 40 beats/min), and atrioventricular block. The optional drug may be atenolol which is not metabolized by liver enzymes and is excreted unchanged [47].

Cytochrome P450 metabolizes the oral anticoagulant warfarin. Simultaneous prescription of warfarin and inhibitors of this cytochrome (amiodarone, some antibiotics) is a common cause of adverse reactions in elderly patients [15].

Predictable pharmacodynamic interaction is widely used in combination therapy of various diseases. In particular, combinations of ACE and diuretics, ACE and calcium channel blockers, angiotensin II receptor blockers and diuretics are effective in the treatment of hypertension in elderly patients [48, 49, 50].

At the same time, the pharmacodynamic interaction can lead to the decrease in the effectiveness of drug therapy and the development of undesirable side reactions, which requires special attention to the choice of individual drugs [51, 52, 53, 54, 55].

The decrease in the effectiveness of ACE inhibitors in elderly patients with simultaneous prescription of non-steroidal anti-inflammatory drugs was found [30].

A number of authors note a significant incidence of hyperkalemia in elderly patients with simultaneous administration of ACE and potassium-preserving diuretics [54, 55].

The simultaneous prescription of beta-blockers and hypoglycemic drugs may increase the effect of the latter and lead to the development of hyperglycemic coma in patients of older age groups [53].

Age-related changes in the pharmacodynamics and pharmacokinetics of drugs significantly reduce the effectiveness and safety in old age [56].

Conclusion

In order to optimize drug therapy for elderly and senile patients it is necessary to prescribe to patients individually reduced doses especially of those drugs that increase sensitivity with aging. Taking into consideration the slowing down of drug metabolism and the lengthening of their half-life in old age, it is necessary to increase the intervals between the drug administration. When prescribing several drugs, it is necessary to consider their possible interaction and its effect on the course of the disease.

It is necessary to proceed from the features of pharmacokinetics and pharmacodynamics of specific groups of drugs.

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Information about Authors:

Liana P. Kuprash - DSc (Medicine), Head of the Geriatric Pharmacology Laboratory of the State Institution "D. F. Chebotarev Institute of Gerontology NAMS of Ukraine"; <https://orcid.org/0000-0001-8196-751X>

Svetlana A. Gudarenko - Researcher of the Laboratory of Geriatric Pharmacology of the State Institution "D. F. Chebotarev Institute of Gerontology NAMS of Ukraine"

Olena V. Kuprash - MD, PhD (Medicine), Department of Clinical and Epidemiological Cardiology of the State Institution "D. F. Chebotarev Institute of Gerontology NAMS of Ukraine"

Nadiya O. Gorchakova - DSc (Medicine), Prof. of the Department of Pharmacology with a course in clinical pharmacology of the Bogomolets National Medical University

Olena V. Khodakivska - MD, PhD (Medicine), Bogomolets National Medical University

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