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Review Article

Features of Pharmacotherapy in Elderly and Senile Individuals: Risks, Pharmacokinetics and Safety

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Abstract

When treating elderly and senile people, it is necessary to take into account that medicinal therapy should be only one of the links in the complex of therapeutic measures. Self-medication is unacceptable for elderly and senile people. It often contributes to the further development of diseases, which often turn into severe, incurable forms. The risk of adverse reactions in people over 60 years of age is 1.5 to 2 times higher than in people aged 30 to 40, and the risk of hospitalization for elderly people due to complications from drug therapy is 1.5 to 2 times higher. The highest number of deaths related to drug therapy occurs in people aged 80 to 90.

Keywords: geriatrics; pharmacokinetics of aging; geriatric pharmacotherapy; drug interactions

Introduction

When administering drug therapy to elderly and senile individuals, there is an increased risk of toxic manifestations of drug accumulation, undesirable biological effects of drugs on the body, interactions between different drugs, and persistent hypersensitivity to a drug, which is often caused by previous years of drug use.

As the human body ages, both the pharmacokinetics and pharmacodynamics of drugs change, and they are impaired at various levels: absorption in the gastrointestinal tract, hepatic metabolism, biological transport, excretion, and receptor sensitivity and response. Many drugs have an increased effect in older people due to decreased clearance of the drug, which leads to an increase in its concentration in the serum [1].

Absorption. The oral route of drug administration is the most commonly used in geriatric practice.

Physiological age-related changes in the gastrointestinal tract, which are highly individual in older adults, can cause significant variations in the absorption of orally administered drugs. Both the rate and efficiency of the absorption process may be affected.

Studies of the gastrointestinal tract in practically healthy elderly and senile individuals show that the hypokinesia of the stomach and intestines progresses with age. The overall tone of various parts of the stomach naturally decreases during the aging process. This often leads to a decrease in the evacuation capacity of the stomach and a slower elimination of medications into the intestines. Delayed gastric emptying affects drugs that are unstable in acidic environments, as it postpones their arrival at the preferred absorption site [1, 2]. Enteric-coated medications, such as aspirin, may release early in the stomach due to altered absorption linked to increased gastric pH in geriatric patients, raising the risk of gastrointestinal (GI) ADEs [1, 3]. Since the small intestine is the site of maximum absorption due to its larger mucosal surface compared to the stomach and colon, a slower evacuation of medications from the stomach reduces the rate of their absorption.

Drugs with a short half-life are particularly sensitive to delayed gastric emptying. A decrease in the rate of drug evacuation, combined with normal or accelerated elimination, may prevent the achievement of therapeutic concentrations in the plasma and tissues. Delayed gastric emptying may have an undesirable effect on acid-resistant drugs (e.g., penicillin).

The decrease in the rate of drug absorption in older individuals may be due to the atrophic processes associated with aging in the gastric wall, changes in the gastric vessels, and a decrease in the mesenteric blood flow.

As people age, the secretory function of the stomach decreases. In older adults, hypochlorhydria and achlorhydria occur in almost 50% of cases. Along with a decrease in acid production, the production and activity of enzymes also change significantly. The pH of the gastric contents does not seem to have a significant impact on the absorption of drugs, as it occurs primarily in the intestines, but the solubility of certain drugs (such as tetracyclines) is highly dependent on an acidic PH. The degree of solubility of a drug in the stomach largely determines the rate and volume of its absorption in the small intestine.

Changes in the rate of drug absorption in elderly and especially senile individuals are also observed when drugs are administered subcutaneously or intramuscularly. This is due to a decrease in blood flow velocity and changes in the permeability of capillary walls. As a result, the effects of these drugs are often observed later and at a lower intensity compared to younger individuals.

Distribution of drugs in the body. The aging process can affect the distribution of drugs in the body in various ways. At this stage of pharmacokinetics, the rate of accumulation of drugs by tissues is greatly influenced by the decrease in cardiac output, the age-related characteristics of blood supply to various organs and systems, the rate of plasma flow, and the permeability of cell membranes. These changes, which gradually progress with aging and are not uniform in different tissues and organs, can lead to diverse distributions and interactions of drugs in the body. The dynamics of drug metabolism and elimination are largely dependent on the degree of impaired blood supply to the liver and kidneys.

The shifts in the protein composition of the blood observed during aging, due to a decrease in the content of albumins, lead to a decrease in the ability of the substance to bind to the blood protein. At the same time, the concentration of unbound substance, which is free to diffuse into the body's tissues, remains high. Thus, the decrease in the amount of the albumin fraction in the plasma proteins of older individuals makes them more susceptible to the effects of drug therapy and the development of drug intoxication, especially when multiple drugs are used.

With aging, body composition changes significantly — in the period from 25 to 60 years, body muscle mass decreases by 20%, the amount of fat increases by 10-20%, the amount of water decreases by 10-15%; after 75 years, the water content in the body decreases by 18-20%. This altered composition affects the distribution volume of hydrophilic and lipophilic drugs, causing higher concentrations of hydrophilic drugs and prolonging the elimination half-life of lipophilic drugs. Lipophilic drugs like chlordiazepoxide, morphine, and amiodarone tend to have a larger distribution volume in geriatric patients, creating a larger reservoir within the body [1]. Because drug clearance is proportional to distribution volume, lipophilic drugs exhibit longer clearance times, resulting in extended durations of action and increased risk of residual effects, as observed with drugs like acitretin and first-generation H1-antihistamines (diphenhydramine) used for chronic hives [1, 4]. Conversely, hydrophilic drugs such as digoxin, lithium, ethanol, and theophylline have a reduced distribution volume, leading to higher plasma concentrations and necessitating smaller doses to achieve therapeutic levels [1, 5, 6]. In contrast, lipid-soluble nonpolar drugs have increased volumes of distribution with age, leading to prolonged half-lives. This has been observed in drugs like diazepam, thiopentone, lignocaine, and chlormethiazole [1, 5-7].

As a rule, the mass of parenchymal organs decreases. In this regard, it is impossible to calculate the dose of the drug based on the total body weight.

It is known that drugs quickly penetrate into parenchymal organs, such as the heart, brain, liver, kidneys, and other well-perfused tissues, but they penetrate more slowly into muscles and even more slowly into adipose tissue. The latter is slower than the parenchymal organs in eliminating drugs and acts as a reservoir for their continued effects.

Metabolism of drugs. During the aging process, the structure and function of the liver, which is the main site of biological transformation of drugs, undergo a number of significant changes due to age-related atrophy and changes in the number and size of many cellular elements in the parenchyma. The liver's mass decreases by 10-15%. Regional blood circulation is significantly altered, and many of the liver's functions, including protein synthesis and antitoxicity, which play an important role in the normal metabolism of drugs, are reduced. Pathological liver damage in the elderly further reduces its synthetic and detoxifying functions. Due to the decrease in hepatic drug metabolism with aging, the liver often fails to reduce the high concentration of unbound drug to a normal therapeutic level, which can lead to drug intoxication. Reduced hepatic blood flow and decreased liver mass are the key factors contributing to diminished first-pass metabolism in geriatrics [1, 8-15].

Excretion of metabolites. The last phase of pharmacokinetics is the excretion of drug metabolites, which is primarily carried out by the kidneys. In older adults, the excretory function of the kidneys gradually decreases. The weakening of renal circulation is caused by the dilation of glomerular vessels. In healthy individuals, the effective renal blood flow decreases by more than half, averaging only 42% compared to younger individuals. By advanced age, the nitrogen excretion function of the kidneys decreases by more than three times. Age-related decrease in renal hemodynamics and the number of nephrons affects the effectiveness of drug excretion. Given the impairment of liver metabolism and renal excretory function, the initial dosage of drugs should be reduced to one-third to two-thirds of the adult dose.

A number of drugs are excreted from the body mainly by the kidneys in their unchanged form or as active metabolites; when they are prescribed, the functional capacity of the kidneys should be evaluated beforehand. Treatment of the elderly should be started with the lowest of the recommended doses, and then adjusted according to the clinical effect and the level of the drug in the blood. These drugs include: penicillin's (large doses), digoxin, aminoglycosides, allopurinol, Novocain, cephalosporins (ceporin, cefamizin, etc.), methyldopa (dopegit), etambutol.

Chlorpropamide, sulfanilamide's, tetracyclines, furadonin should not be prescribed to elderly and old people with significant renal impairment, as they are not effective in this case and have pronounced side effects.

The reaction of cells and tissues. The failure, and sometimes the negative effect, of drug therapy used in geriatric practice may be a consequence of changes in cell reactivity, their exhaustion, caused by the aging of the body and the superimposition of a pathological process that contributes to involution.

With aging, against the background of increased sensitivity, the reactivity of cells and tissues decreases, which is an expression of a reduction in the range of adaptive possibilities.

These data largely explain the origin of the inappropriate reactions in older people that can be observed when medications are administered. The negative effects, paradoxical reactions, and qualitative changes in tissue response are largely due to the lack of parallelism in changes in sensitivity, reactivity, and endurance, especially in cases where increased sensitivity is accompanied by reduced reactivity. This is why increasing the dosage of medications in older patients does not always provide a therapeutic effect and can relatively easily lead to adverse reactions. This is especially true for cardiac glycosides, nitroglycerin, sympathomimetics, and some other drugs.

Drug interactions. The problem of drug interactions is becoming increasingly relevant in modern medicine as new drugs are introduced, and the number of drugs has been rapidly increasing in recent years.

Elderly and senile age is not a reason to avoid using combination drug therapy, but the doctor must be aware of the increased risk associated with this therapy, as the line between the active and dangerous zones of drug action becomes narrower with age. The frequency of adverse reactions increases as the number of drugs used simultaneously increases, and it also increases with the age of the patient.

Absorption of drugs and motor activity of the digestive tract. Interactions between drugs at the level of absorption in the gastrointestinal tract can be very diverse. First of all, this is a change in absorption due to impaired motor activity of the stomach and intestines, and inhibition of absorption of one drug as a result of the inhibitory effect of another drug. The slower movement and absorption in the gastrointestinal tract of older individuals and the longer interaction between drugs in a specific part of the gastrointestinal tract can lead to metabolic transformations and subsequent inactivation of one drug before it is absorbed. In cases of achlorhydria, the absorption of weak acids (such as salicylic acid) and barbiturates is reduced. Hypochlorhydria, a condition more common in older adults, may reduce the absorption of weakly alkaline drugs such as ketoconazole [16, 17]. The habitual use of laxatives by elderly and senile individuals can lead to increased potassium excretion, which should be taken into account when treating patients with digitalis, especially when combined with diuretics. Drugs like levodopa show a notable increase in absorption rates in geriatric patients, likely due to reduced dopa-decarboxylase in the gastric mucosa [18].

Medications and food. The absorption of medications and their interactions in the gastrointestinal tract can also be affected by their interaction with food components.

An example of an undesirable interaction between food and medication is the simultaneous administration of tetracycline with milk, which contains high levels of calcium, which can form insoluble complexes with this antibiotic. Acidic fruit and vegetable juices can also reduce the effectiveness of acid-resistant antibiotics (such as ampicillin, erythromycin, etc.) when taken with them. Sweetening medications with syrups slows down the absorption of amidopyrine, calcium chloride, isoniazid, tetracycline, and others. Food slows down the absorption of many antibiotics and sulfanilamide's. A meal before administration of acetylsalicylic acid causes a sharp decrease in its level in the blood compared to administration on an empty stomach.

Medications and alcohol. In geriatric practice, special attention should be paid to the interaction between alcoholic beverages and medications. Alcohol can potentiate the effects of barbiturates, which should not be prescribed to the elderly and senile, as well as amines, tricyclic antidepressants, and benzodiazepine derivatives (elenium, seduxen, tazepam, etc.). The toxicity of barbiturates can increase by more than 50%. Alcohol can also significantly enhance the side effects of acetylsalicylic acid. Therefore, in the elderly and senile age, the combination of aspirin with vodka should be avoided, which is quite often used as a "home remedy" for colds. For patients with diabetes, alcohol is dangerous when taking butamid, as it reduces its effect and makes it essentially ineffective.

Massive dosages. One of the main principles of geriatric pharmacology is the need to avoid large doses of medications. In the elderly and senile age, it is especially difficult to tolerate large doses of medications, which are often as inappropriate as large physical and emotional loads, food excesses, etc. These require the mobilization of significant reserves of the body's adaptive mechanisms, which are usually significantly reduced in older adults. The potentiation of the effects of medications by alcohol is one of these loads that can lead to very undesirable, sometimes tragic, results.

Two or more medications at the same time. If two medications are present in the blood at the same time, the medication with a higher ability to bind to proteins will displace a portion of the other medication and make it biologically active. Therefore, the administration of two medications without a pharmacological or clinical justification may result in an overdose or toxic effects, even if both medications are administered at normal doses. This risk is significantly increased when multiple medications are administered. In this case, the specific relationship between drugs and their interaction with protein receptors often leads to unexpected, often undesirable, and sometimes dangerous reactions.

An example of such reactions is the interaction between digitalis or strophanthin and calcium supplements, which are often prescribed for older adults with senile osteoporosis. Calcium can displace both digitalis and strophanthin from their protein-binding sites, leading to overdoses of these medications. Barbiturates can also accelerate the metabolism of digitalis and reduce its effectiveness.

Medications and cellular (tissue) receptors.

Interactions between medications can also occur in the pharmacodynamic phase, when their metabolites affect the peripheral receptors of various organ tissues. The nature of this interaction determines the final effect of the substance, which depends on its ability to bind to receptors, their reactivity, and sensitivity. Thus, the therapeutic effect is determined not only by the concentration of the free, non-protein-bound part of the drug, but also by the specific response of tissues, organs, systems, and the entire human body, which vary significantly with age.

Drug interactions can change the biological activity of one or more drugs due to competitive effects at the receptor level. Due to the age-related characteristics of the aging body's response to drugs, these changes and their clinical manifestations can be quite unexpected and undesirable in older adults during the treatment of a pathological process.

In many cases, these changes may be evident, such as hemorrhagic events, lack of response to antihypertensive drugs, excessive sedation, and others. However, they are often overlooked. For elderly people, latent, mild-symptom, and prolonged course of diseases is typical. The same is true for drug interaction reactions. Usually, they occur, being masked by the general picture of the disease, and, remaining unrecognized, affect the general condition of patients.

2.5. Principles Of Pharmacotherapy

The main principle of geriatric pharmacotherapy is the more cautious use of drugs in the treatment of elderly and old people than young people. This position receives new justifications in pharmacological studies, everyday clinical observations. The position put forward in geriatrics about the need to assess all other possibilities of influencing the sick body of an old person before prescribing drug therapy, not to use drugs if other therapy is possible, deserves great attention.

Everyday experience shows that it is not the presence of pronounced organic changes, but rather unfavorable social factors, that often cause an elderly or old person to feel ill. In such cases, the use of medication is often unnecessary and sometimes even harmful. In geriatric practice, it is crucial to pay attention not only to the patient's physical condition but also to their mental status and the external factors that can affect their well-being, sleep, mood, and desire to live.

In some cases, medications can actually contribute to the development of a disease. Long-term drug treatment requires periodic review of the pharmacotherapy regimen to reduce the list of medications.

When conducting drug therapy for the elderly and senile, the factor of full confidence in the therapeutic properties of drugs, as well as knowledge of their effect on the body during long-term use, is especially important. The side effects of drugs on individuals who have reached retirement age, and especially on the elderly, are often unpredictable. As a general principle, geriatrics should avoid medications with anticholinergic effects whenever possible [1, 19, 20].

The objectives of clinical pharmacology include assessing the indications for pharmacotherapy, not only for new and still poorly studied drugs, but also for well-established drugs, especially when they are used in combination and over many months and years.

The unjustified prescription of medications in geriatric practice is caused not only by a lack of knowledge about the pharmacological effects on the elderly patient's body, but also by a lack of knowledge about physiological age-related norms. Not only is hypodiagnosis (the failure to recognize existing diseases or pathological processes) harmful, but so is hyperdiagnosis (the misinterpretation of age-related norms, functional tests, and clinical analyses as symptoms of a disease) and the resulting irrational use of medication.

Special attention should be paid to the regular intake of prescribed medications. People of older age, especially the elderly, often forget to take their medications or take them again after a short period of time. Therefore, in a hospital setting, the nurse should personally administer the medication prescribed by the doctor. At home, the daily dose of the medication should be stored so that the patient can see how many times they have taken it based on the remaining powders or tablets. In geriatric practice, it is convenient to use colored tablets or capsules. When prescribing the simultaneous intake of several drugs at home, it is advisable to place them in the lids of medicine bottles in the morning, with cut-out circles of paper of different colors or other markings on the bottom. If possible, liquid medications should be avoided. Due to poor eyesight and hand tremors, it is often difficult for patients to accurately dose medications, especially the number of drops. Additionally, the lack of precise control over the packaging can lead to leaks and changes in the concentration of the medication due to evaporation, microbial contamination, and degradation.

The basic principles and features of drug therapy in geriatric practice:

1) the risk of adverse effects on the organs of drugs, due to age-related features, which are often aggravated by changes associated with pathological processes, is significantly higher in elderly and old people than in younger people;

2) in old age, adaptation to loads of any kind, including natural toxic metabolites and drugs, is significantly reduced. In this regard, the resistance to intoxication in the old body is less and even a small intoxication is dangerous;

3) polypragmasia (multiple drug therapy) is unacceptable. It is necessary to limit the number of medications as much as possible, using their targeted effect on the main disease. The method of taking medications should be as simple as possible. When prescribing medications, the mental health of the elderly person and their social conditions, as well as the possibility of care, should be taken into account. Great attention should be paid to observing the intervals between medication doses;

4) the most important rule is individualization of doses; reduced doses of medications are recommended, especially at the beginning of treatment. By gradually increasing the doses, it is possible to establish tolerance to the medication. This is particularly important for cardiac glycosides, sedatives, antihypertensive medications, and antipsychotics. The initial doses of these medications should be reduced by half compared to the doses used for middle-aged individuals. Once the therapeutic effect is achieved, the dose should be reduced and a maintenance dose should be determined, which is usually lower than in adults.

5) treatment with antibiotics and antibacterial chemotherapy drugs should be carried out at normal or slightly reduced dosages, according to the general rules. It should be noted that the risk of intoxication and side effects of these substances on the elderly and senile body is higher, especially if they are not adequately supplied with vitamins, especially B vitamins;

6) it is important to consider not only the nutritional value of the patient's diet, but also their water and salt intake, as well as the amount of urine produced. This is particularly important due to the frequent underconsumption of fluids by the elderly, which can lead to drug intoxication.

7) long-term use of many medications, such as sedatives, painkillers, and sleeping pills, can lead to addiction and cause patients to increase their doses, which can result in drug-related intoxication. It is recommended to use these medications for a short period of time, frequently replace them with similar medications, and take breaks between doses when possible.

8) To prevent toxic effects and enhance the effectiveness of medications, it is advisable to use a combination of pharmacological agents in small doses that have similar therapeutic effects and complement each other, but target different aspects of the body's self-regulation.

9) Inborn or acquired specific sensitivity to certain drugs can be observed in all age groups. Drug allergies are a common complication in older age groups;

10) The so-called geriatric drugs, general stimulants aimed at maintaining metabolic processes and functions, and above all, appropriate complex vitamin therapy, have a certain significance in the prevention and treatment of premature aging and can be combined with a number of other drugs in the treatment of diseases. Vitamin therapy should be considered as a factor that reduces the risk of drug intoxication and other side effects.

Conclusion

Pharmacotherapy in the elderly requires particular caution due to age-related changes in pharmacokinetics, which increases the risk of toxic effects and drug interactions. Initial doses should be reduced, and polypharmacy should be avoided, as adaptive mechanisms are weakened in old age. Treatment should be initiated with minimal doses under clinical supervision, avoiding self-medication and taking into account the patient's individual response.

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