



Pharmacodynamics and pharmacokinetics in the elderly

*Aging is not disease and is not treatable by medicaments.
Many older people admitted to hospital or reviewed during
long term hospitalization improved greatly, when the drug
regimen that they had been taking, was stopped.*
(WHO)

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Abstract

The paper deals with changes in pharmacodynamics (the study of what the drug does to the body) and pharmacokinetics (the study of what the body does to the drug) in the elderly. Elderly population takes 25–30 per cent of drugs taken by total population. In the elderly pharmacodynamics and pharmacokinetics are altered. According to pharmacokinetics, gastric juice pH is elevated which influences drug solubility and absorption. Drug distribution is decreased in the elderly because of decreased cardiac output, increased peripheral vascular resistance, diminished blood flow in the liver and the kidneys, reduced total amount of water in the body. Drug metabolism and biotransformation mainly take place in the liver and is reduced very often. Drug elimination is reduced very often because of reduced renal reserve: creatinine clearance is reduced in the elderly in spite of the fact that the serum values remaining in the normal range. Pharmacodynamics could be altered in the elderly, as a consequences of receptor binding, of postreceptor effects, and of chemical interactions. The clinical effects of drug concentrations could be greater or smaller than those in middle-aged or younger persons.

INTRODUCTION

Elderly population takes 25–30 per cent of drugs taken by total population. In the elderly pharmacodynamics and pharmacokinetics are altered. Pharmacodynamics is the study of what the drug does to the body, and pharmacokinetics is the study of what the body does to the drug (1–11).

Gastric juice pH is elevated which influences drug solubility and absorption. Atrophic gastritis occurs, absorption surface diminishes, gastric contents are more slowly discharged, intestinal motility decreases, intestinal diverticulosis is present. Drugs absorbed by passive diffusion are freely resorbed (e.g. indomethacin) whereas the absorption of drugs that are actively transported is slower. Passive diffusion is quicker if the drug is soluble in the lipids. There are two important factors of drug absorption from the gastrointestinal tract: constant absorption rate and bioavailability of the drug. Absorption from the

bowel depends also on the drug conversion by the bacteria present in the gastrointestinal tract.

Drug distribution is decreased in the elderly. Reasons for this are numerous: decreased cardiac output, increased peripheral vascular resistance, diminished blood flow in the liver and the kidneys, reduced total amount of water in the body. The serum albumin concentration is also reduced during aging, by 30 per cent in comparison to younger age. This is important because many drugs are linked on plasma albumins and lower concentration of serum albumins means higher pharmacological activity of the drug. The volume of distribution e.g. the drug concentration in the body divided by its concentration in the blood, is lowered by the old age. Hydrophylic drugs have a decreased volume of distribution, and lipophylic ones an increased volume of distribution (1, 5–11).

Drug metabolism and biotransformation mainly take place in the liver. This process is reduced very often in the elderly. Besides the liver, this process takes place in the lungs, in the plasma, in the gastrointestinal tract mucosa, and in the kidneys. The microsomal liver activity is reduced. Here the drug is changed into a less active or inactive substance, rarely into a more active one. The processes of the phase 1. of drug metabolism in the liver (hydroxylation, N-dealkylation, N-demethylation, sulfoxidation, nitroreduction and hydrolysis) are diminished. It seems that the processes of the phase 2. (conjugation) does not change with the old age. Examples of the drugs of the 1.phase are: propranolol, benzodiazepines etc. Drug clearance by the liver with digoxin, diazepam can be reduced, average with quinidine, prazosine, or increased with verapamil, nifedipine, doxepine. Drug elimination half-life becomes longer with the old age (1,5,12–16).

Drug elimination takes place mainly in the kidneys: by glomerular filtration, tubular excretion or by both ways. Due to reduced renal reserve, creatinine clearance is reduced during in the elderly in spite of the fact that the serum values remaining in the normal range. Many drugs are weak acids or weak bases. They can be soluble in water, lipids, in tubular fluid-like ions or undissociated acid soluble in lipids. Tubular cells behave as a lipid membrane. Therefore the undissociated drug molecules will diffuse back faster. The back diffusion of the drug depends on the urine pH. In alkaline urine the elimination of some drugs is reduced and their action is longer, for example amphetamine. Some drugs reduce renal blood flow, for instance propranolol, and should therefore be avoided in elderly person with reduced creatinine clearance. Tubular function also decline with age, so that biological half-life of penicilline in the elderly is two times longer than in younger, the same being valid for cephalosporins, probenecid etc. (1, 5, 8, 10, 11).

In the elderly non-fat body mass is reduced, as well as the total amount of body water, which reduces the drug distribution volume of hydrosoluble drugs. A relative increase of body fats is present. Plasma albumin concentration is decreased, which causes the alteration of

volume of distribution. Heart reserve is decreased, which increases the danger of congestive heart failure in case of the use of fluid retaining drugs or of those that have negative inotropic action. Metabolizing capacity of the liver, lungs vital capacity and renal reserve are reduced. Because of that, some drugs that are cleared by those organs have to be used in reduced doses in avoid of accumulation and possible side effects.

Pharmacodynamics could be altered in the elderly, as a consequences of receptor binding, of postreceptor effects, and of chemical interactions. The clinical effects of drug concentrations could be greater or smaller than those in middle-aged or younger persons.

DRUG INTERACTIONS

Many drugs that bind to plasma albumins are responsible for the occurrence of drug interactions when they free themselves from the albumin-drug complex. Drug interactions are more frequent in the elderly as microsomal hepatic enzymes are inhibited because of polypharmacy (polypragmasia). Polypharmacy is the use of multiple drugs. The interactions of antihypertensives and general anesthetics are well known, which may lead to arterial hypotension. Another cause for drug interactions, apart from polypharmacy, is a modified drug effect also. The greater number of drugs an elderly patient takes, the great danger of interaction occurs. If two drugs are taken simultaneously by an elderly person, prospect for an interaction occurrence are almost 6 per cent. If 5 drugs are taken, these chances amount up to 50 per cent, and if 8 or more drugs are taken, prospects for an interaction are near 100 per cent. It should be therefore striven to limit the number of drugs taken by an elderly patient to no more than three: the lowest number of used drugs should be striven at. Drug interactions should occur at any level, from absorption to elimination. Well-known is the competition on the receptor when several drugs are applied simultaneously. This is often used for therapeutic purpose, like the use of naloxone in opiate intoxication, since it has a great affinity for opiate receptors (8, 11).

ADVERSE DRUG REACTIONS

Adverse drug reactions occur about twice as often in the elderly, who are more sensitive to drugs than the younger. The use of morphine as an analgetic, in the elderly could be an example for this. In the elderly a lower doses than in the younger must be applied because the usual dose provokes the central nervous system depression. β adrenergic receptors are less sensitive to agonists than to antagonists. The bioavailability of drugs with the first pass hepatic metabolism can be both increased and decreased. Baroreceptor function is often altered in the old age which is directly connected with the use of antihypertensives. Adverse drug reactions are more frequent in an elderly patient, because of careless clinical estimation of his clinical condition, which can result in inadequate chosen drug, or because of overdosing of the

drug caused by numerous reasons. Another cause of adverse drug reactions is insufficient control of the effect of the drugs used for a longer period of time, e.g. digitalis glycosides (10, 11, 14, 16).

POLYPHARMACY

Polypharmacy is often a problem in the elderly, who usually take 4 to 5 different drugs daily. These patients generally suffer from several diseases simultaneously, with many new disease elements. This imposes adequate and careful dosing. Yet, even when the diagnosis has been adequately established, elderly patients are inadequately managed. Reasons for this are numerous: disrespect for particular alterations in the body of an elderly person, too high dose applied, inadequate treatment of each disease symptoms and disrespect for specific changes in drug effect on the body of an elderly patient. The unjustifiable number of drugs taken by an elderly patient is, according to the data, from 3–12 daily, the significant number being ineffective. An elderly patient who visit many physicians is in danger for polypharmacy. Apart from his general practitioner, rather often a patient consults different specialists, and if the old patient is not approached comprehensively, the number of prescribed drugs will be rather large. Adverse drug reactions are proportional in number to the number of drugs taken. The patient often does take all these drugs. If he makes a selection and takes only some of the many drugs prescribed, he may not harm himself if he drops (by chance) drugs of uncertain efficacy or certain ineffectiveness. On the contrary, he will harm himself, if he stops taking essential drugs, i.e. digitalis glycosides, antihypertensives, calcium-channel blocking agents, anticoagulants etc. (1, 5, 7, 8, 10, 11, 14, 16).

THE PRINCIPLES OF DRUG TRIALS IN THE ELDERLY

In avoid polypharmacy i.e. the use of multiple medications, it is necessary to make the basis guidelines of the clinical pharmacology of the old age using a scientific approach to drug trials and individualized therapy. Polypharmacy in the elderly has to be reduced by eliminating useless drugs, ineffective drugs, unnecessary drugs, ineffective drugs, drugs with duplicate effects, drugs with undesirable side effects. In this field a cost-benefit ratio of health care for elderly patients is important because it is estimated that 25 per cent of all prescribed drugs taken by an elderly patient, is probably unnecessary. Many facts that are often lacking, are necessary when a drug is prescribed to an old patient. Here it must be taken into account that 4 out of 5 elderly patients suffer from at least one of chronic disease. The most common diseases in the elderly for which a new drug is investigated are coronary heart disease, peripheral vascular disease, senile dementia. Drug therapy is particularly present in the elderly suffering from arterial hypertension, congestive heart failure, cardiac arrhythmias, arthrosis, arthritis, pneumonia, osteoporosis, urinary tract infections including prostatic diseases. This must be taken into account when the

patients group in which the new drug will be investigated is selected, considering the patients sample and measuring during the trial (10, 11).

Prior to drug administration in an elderly person, its pharmacokinetics must be analyzed in younger healthy volunteers. The results obtained must be analyzed.

In the elderly not to forget organs and organic systems changes and reduction of ability to excrete drugs: the reduction of renal reserve. It is desirable that the drug is investigated in two groups of patients: one consisting of younger patients aged 21-39 and the other one of elderly patients of chronological ages 65 or more. Elderly of course does not exclude an examinee from the trial. It must be said that the majority of clinical drug trials in elderly persons conducted nowadays have included patients up to 75 years of age; most often the age was even below 70. Of course, examinees should be included in clinical trials, particularly those over 75. This is the way to collect precise informations on drug use in patients over 75.

There are age variances regarding pharmacodynamics (the relation between the clinical effect and the plasma drug level) and pharmacokinetics (movements of drugs from absorption, distribution, binding to plasma albumins, metabolism, and elimination). Concerning the elderly in whom a drug is investigated, the trial should be performed on a small number of patients. Simultaneously the investigation should be performed on the young and the two groups should be compared in order to estimate the difference between the groups. A certain number of elderly patients can be included in phase 2. and 3., although most frequently they take part in phase 3. of therapeutic clinical trial only. It is significant that the drug effect on the body can be observed after only a few doses. Here the dose-dependent effect will be determined. When the drug is investigated simultaneously in the younger and in the elderly, plasma drug level must be analyzed in both groups, in order to determine the differences between the age groups. This trial must be comparative (10,11). The following points must be taken into consideration while clinically investigating drugs in the elderly:

1. The aim of the trial in equal to the one in other age groups. Therapeutic efficacy and relative safety of the new drug in comparison with the pre-existing one must be proved. The patients in whom the new drug is indicated must be particularly selected, optimal dose and side-effects should be found;

2. Types of trial: a double-blind randomized trial is ideal, but it can also be controlled, comparative, open and blind. Most often, phase 3. is performed;

3. The selection of patients is a certain problem, as these patients suffer from several simultaneous diseases. Quite often the trial will be started in the hospital and later the drug will be administered in out-patient units. All other pharmacotherapy must be maximally reduced;

4. Measurements: individualized pharmacotherapy should be striven at. Measurements must result from a precise trial protocol, it must be simple and non-invasive whenever it is possible; the determination of drug concentration in the plasma should be insisted upon.

GENERAL PRINCIPLES OF DRUG THERAPY

Chronic diseases are more frequent in the elderly than in other age groups. Therefore elderly take drugs more frequent, although very often not in a proper way. According to some data, more than 60 per cent of elderly patients take drug inadequately. There are numerous reasons for that, the basic one being polypragmasia. Above 25 per cent of those (60 per cent) elderly patients make serious mistakes in drug therapy. The largest number of administered drugs – the most frequent mistakes are. When a drug is used in an elderly person, the following questions have to be answered: Is the treatment necessary? Is it possible? What are its expected results?

Not all disease symptoms have to be treated. Many chronic diseases cannot be treated with drugs. The drug administered to an elderly patient must be the one with well known adverse effects. It is the fact that in such patients the regularity of taking the therapy is reversely proportionate to the number of drugs he is taking must not to be forgotten. The drug's purpose must be carefully stated orally and in writing, and this aspect must be taken into as much consideration as it should be necessary. In old patients it should be striven to give a single daily dose of, for instance digitalis glycosides, diuretics, corticosteroids etc. The patients attention must also be drawn to the connection between the drug and meals: should the drug be taken before, after or independently from a meal? It is especially important to warn the patient about whether a drug can be taken simultaneously with other drugs, and which drugs can be combined as well as which drugs cannot be combined (e.g. antacids and digitalis glycosides). If we make the drug taking simpler, it is more probable that an older patient will take the drug. Also, if a chronic disease is treated for a long period of time, the same brand name and the same preparation should be prescribed since this is usually how patients recognize the drug: by colour and the preparation (7, 10, 11, 14, 16).

It is important to take care about the drugs package and, if a bottle is used, to make sure that the patient can open it. It is better not to prescribe drops to elderly patients. They will, their eye-sight being worse and hands shaking, probably pour a greater number of drops and risk the adverse drug reactions. Sometimes the old patient cannot take out his drug from the plastic package and therefore does not take the drug. Drugs should always be in the shape of tablets or dragees in bottles with wide cover that opens by turning.

It would be good to write the time of the drug-taking and the dose in a calendar for the old patient. The are

plastic boxes in which a dose necessary once to three times a day for 7 days can be put. This is very handy for an old person. It must be refilled once a week and at the same time it presents therapy control: thus it is immediately obvious if the patient has taken the drugs in appropriate doses. This box had 3 horizontal and 7 vertical walls the name of the day on them.

The patients family must be familiar in details with the therapy, especially when they take care of him. All drugs but those that the patient must take, should be removed from where he can reach them in case he makes a mistake. It would be good too, if the drug is in a paper box or in a bottle, to write its purpose on the package: e.g. for high pressure, for urination, against thrombosis, against urinary infection etc. The problem of drug treatment in the elderly very often means reducing many drugs that the patient has been taking previously. It is also a reason why therapy control is desirable and often necessary in the elderly (5, 10, 11, 14, 16).

REFERENCES

1. ANDRES R, BIERMAN E L, HAZZARD W R 1985 Principles of geriatric medicine, McGraw-Hill, New York.
2. SCHRIER R W (ed.) 1990. Geriatric Medicine. WB Saunders, Philadelphia.
3. DURAKOVIĆ Z, MIŠIGOJ DURAKOVIĆ M, ČOROVIĆ N, ČUBRILO TUREK M, TUREK S, SCHNAPP MANITAŠEVIĆ A 1996 Hospitalization of older and younger patients in a Department of Internal medicine – variety of reasons and outcome. *Collegium Antropologicum* 20: 213–220
4. HALL W J 1999 Update in geriatrics. *Annals of Internal Medicine* 131: 842–849
5. HAZZARD W R, BLASS J P, ETTINGER W H Jr, HALTER J B, OUSLANDER J G (eds) 1999 Principles of geriatric medicine and gerontology, 4.edition. McGraw-Hill, New York.
6. TRESCH D D, ARONOW W S (eds) 1999 Cardiovascular disease in the elderly patient. M. Dekker, New York.
7. BEERS M H, BERKOW R 2000 The Merck manual of geriatrics, 3 ed. Whitehouse, NJ.
8. LANDEFELT C S, PALMER R M, JOHNSON M A, JOHNSON C B, LAONS W L 2004 Current geriatric diagnosis & treatment. Lange/McGraw-Hill, New York.
9. BOWKER L K, PRICE J D, SMITH S C 2006 Oxford handbook of geriatric medicine. Oxford Univ. Press.
10. DURAKOVIĆ Z (ed) 2007 Geriatric – Medicine for the elderly (in Croatian), CT-poslovne informacije, Zagreb.
11. DURAKOVIĆ Z (ed) 2011 Geriatric Pharmacotherapy. CT-poslovne informacije, Zagreb.
12. DURAKOVIĆ Z, MIŠIGOJ DURAKOVIĆ M, ČOROVIĆ N, PEZEROVIĆ DŽ, GAŠPAROVIĆ V, ČUBRILO TUREK M, TUREK S, ĐUREK M, NAUMOVSKI MIHALIĆ M, DE SYO D 1988 Hypothermia and acute renal failure in the elderly. *Collegium Antropologicum* 22: 5–140
13. DURAKOVIĆ Z, MIŠIGOJ DURAKOVIĆ M, ČOROVIĆ N, ČUBRILO TUREK M 2000 Urban hypothermia and hyperglycaemia in the elderly. *Collegium Antropologicum* 24: 405–409
14. CAYLEY A C D 1987 Hospital geriatric medicine, Arnold, G.B.
15. MIŠIGOJ DURAKOVIĆ M (ed.) 2003 Exercise and health (in slovenian). The Faculty of the physical culture and the Department of sport in Slovenia, Ljubljana.
16. SLOAN R W 1986 Practical geriatric therapeutics. Ordell, USA.