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# PHARMACOKINETIC AND PHARMACODYNAMIC CHANGES IN ELDERLY PEOPLE

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## ABSTRACT

In this century, aging of a population has emerged as a major demographic worldwide trend. Many changes in physiological and functional capacities of the body occur with old age. This can affect pharmacokinetic (PK) and pharmacodynamic (PD) status of drugs in elderly people, leading to clinically relevant consequences with regard to safety and efficacy. Increasing prevalence of diseases, as well as age independent factors like life style can further impact the pharmacological effects of drugs. In addition, there is a risk for modified PK and PD drug-drug interactions (DDIs) due to polypharmacy. This complexes drug therapy in elderly. The aim of this study is to review some PK and PD changes associated with aging and to give some general recommendations for appropriate drug prescribing in order to reach the safety use of drug therapy in elderly patients.

**KEYWARDS:** Aging, drug-drug interactions, elderly people, pharmacokinetic and pharmacodynamic changes.

## INTRODUCTION

Aging reflects all the changes that occur over the course of life, but in common usage, aging is often used to only mean senescence.[1] Usually, elderly is defined by a chronological age of 65 years or older.[2] Aging is characterized by a progressive changing in physiological and functional capacities of the human body,[3] reduction in homeostatic mechanisms, and altered response to receptor stimulation.[4] This might alter the pharmacokinetic (PK) as well as the pharmacodynamic (PD) of drugs, leading to clinically relevant consequences with regard to safty and efficacy. The risk of adverse drug reactions (ADRs) can be increased. Increasing prevalence for one or more chronic disease conditions, morbidity and co-morbidity in elderly as well as age independent factors like life style (e.g. smoking), genetic and environmental factors can further impact the pharmacological effect of drugs.[3,5,6] With the rising likelihood of polypharmacy as a result of different chronic disease conditions; the risk for modified PK and PD effects due to drug-drug interactions (DDIs) is adding further complexity to the drug therapy.[6] Drug drug interactions (DDIs) can be PK or PD. These DDIs can adversely impact elderly people.[7] The age-related physiological changes that affect the PK profile can occur during drug absorption, metabolism, distribution and elimination (Table 1). Whereas, age-related changes in PD may occur at the receptor or signal-transduction level, or homeostatic mechanisms may be attenuated (Table 2).

The aim of this study is to review some PK and PD changes associated with aging and to give some general recommendations for appropriate drug prescribing in order to reach the safety use of drug therapy in elderly patients.

### Definition of Aging and elderly person

When broadly defined, aging refers to all time-associated events that occur during the life span of an organism. During this time, many changes occur in the physiologic processes. These changes may be beneficial, neutral, or deteriorative. During the developmental period of life, most changes are tend to be beneficial. However, during the post maturational period of life; most changes are detrimental, although some may be neutral such as graying of the hair. The term 'senescence" is used to specifically denote this post maturational deterioration. Senescence is defined as the deteriorative changes with time during post maturational life that underlie an increasing vulnerability to challenges, thereby decreasing the ability of the organism to survive. Although senescence is a subset of aging, in common usage, aging is often used to only mean senescence.[1]

Most developed world countries have accepted the chronological age of 65 years as a definition of elderly person. This is the age at which one can begin to receive pension benefits. At the moment, there is no United Nations (U.N.) standard numerical criterion, but the U.N. agreed cutoff is 60+ years to refer to the elderly population.[8]

Definitions of old age in developing countries fell into three main categories: chronology; change in social role (e.g. change in work patterns, adults status of children and menopause); and change in capabilities (e.g. invalid status, senility and change in physical characteristics).[9] Results from cultural analysis of old age suggested that change in social role is the predominant means of defining old age.[8]

**Demographics of aging**

The world's population is now aging at an unprecedented rate. Declining fertility and improved health and longevity have generated rising numbers and proportions of the elderly population in most of the world.[10] Since 1950, the proportion of elderly persons (≥ 60 years old) has been rising steadily, passing from 8 % in 1950 to 11 % in 2007, and is expected to reach 22 % in 2050.[11]

As we move through the first decade of the twenty-first century, population aging has emerged as a major demographic worldwide trend. People aged 65 and over will soon outnumber children under the age of 5 for the first time in history. Life expectancy is increasing in most countries, and the number of the oldest old (80 and over) is projected to increase 233 % between 2008 and 2040, compared with 160 % of the population aged 65 and over and 33 % of the total population of all ages.[10] In the less developed regions, elderly persons account today for just 8 % of the population, but by 2050 they are expected to account for a fifth of the population.[11]

**Biology of aging**

Aging entails a gradual decrease in physiological fitness and reduced ability to respond to environmental demands. The reduction in homeostatic capabilities is a fundamental feature of aging, but the decline in functional reserve varies markedly between elderly persons.[12]

Very old individuals tend to become frail, a syndrome that includes loss of skeletal muscle mass as well as neuroendocrine and immune dysfunctions.[13] Because of these changes, elderly people are increasingly prone to diseases and multi-morbidity. Between the ages of 20 and 80 years there is a 90% loss of blood vessel distensibility, which together with enhanced intimal thickness and endothelial dysfunction appears to be responsible for the increase of systolic blood pressure and work load of the left ventricle. Renal, hepatic, and to a lesser degree cerebral blood flow declines. The increased stiffness of the left ventricle, that is a consequence of loss of myocytes with subsequent hypertrophy of the remaining cells, slows diastolic filling, and cardiac output decreases. Furthermore, normal human aging is associated with a reduction in baroreflex mediated heart rate response to hypotensive stimuli.[14]

In the endocrine system, the responsiveness to and the serum levels of many hormones are decreased. The prevalence of hypothyroidism increases in elderly people.[15] Changes in endocrine systems also include menopause in women,[16] androgen deficiency in men,[17] decline in growth hormone,[18] and increased incidence of type 2 diabetes.[19]

The susceptibility for infectious diseases and the emergence of tumors is increased in elderly people; possibly because of a decline in the function of the immune system. While reactivity against foreign antigens drops significantly in old age, autoimmune reactions paradoxically, increase.[20]

**Pharmacokinetic (PK) changes in elderly people**

**Drug absorption**

Drug absorption can be influenced by age-related changes in the gastric and intestinal physiology, the membrane permeability or drug transport and the gastrointestinal blood flow. The overall surface of the intestinal epithelium, splanchnic blood flow and gastric acid secretion decrease with age.[3] A decline in gastric emptying of liquids and mixed meals is most likely to occur as a function of increasing age. Changing in the small intestinal motility do not occur until an age of 80 years and beyond. The colonic motility and the anorectal functioning are assumed to change with age as both, constipation as well as fecal incontinence is frequently seen in elderly people.[21] These changes appear to be related to sensory losses due to region-specific loss of neurons.[22] The decrease in gastric and intestinal motility present in the elderly may be a factor that exacerbates interactions. In theory, opioid and cholinergic antagonists, which tend to decrease gastric emptying and gastrointestinal transit, could more significantly restrict the absorption of other drugs in elderly subjects due to an already compromised basal motility.[23] One example of such interactions occurs between anticholinergic drugs which used in the control of movement disorders and levodopa. They reduce bioavailability of levodopa by 50%.[24] The gastric pH can increase with age due to an increasing incidence of achlorhydria. This can lead to an altered bioavailability of pH sensitive drugs or drugs with a pH dependent solubility.[25] Ketoprofen for example exhibited a poor absorption from elderly people with achlorhydria and gastric pH of >5 compared to elderly people with gastric pH < 5. When taken together with acidic juice, the ketoprofen absorption in achlorhydria patient was equivalent to its absorption in elderly people with a gastric pH < 5.[26] O'Connor-Semmes et al. showed that in the presence of ranitidine, the AUC of triazolam was 10% higher in adults < 60 years old and 30% higher in those who were older than that. Higher gastric pH achieved by the elderly with ranitidine probably facilitated the absorption of triazolam, a benzodiazepine sensitive to acid pH.[27] However, a study with ketoconazole, whose ability of dissolution is inversely proportional to pH, revealed that, the rate of hypochlorhydria in the elderly is low (around 5%) and similar to young adults, questioning whether

this factor is as common as it is believed in that population.[26]

Age usually does not affect the absorption of drugs that permeate the intestinal epithelium by passive diffusion in a clinically significant manner. A few exceptions for that was a reduction of the extent or rate of absorption which was shown for only a few drugs (indomethacin, prazosine, digoxin, and ciprofloxacin).[3]

Compounds that permeate the intestinal epithelium by carrier-mediated transport mechanisms may be absorbed at a lower rate in elderly people. Examples are calcium, iron, and vitamins,[28] and may be some nucleoside derivatives and gabapentin, which utilize the active transport or facilitated diffusion to cross this epithelium.[3] The expression of the intestinal plasma membrane calcium pump protein and its inducibility by vitamin D decreases with age in experimental models,[29] which can further impair menopause-related decline in calcium absorption. On the other hand, the absorption of levodopa is increased due to a reduced amount of dopadecarboxylase in the gastric mucosa.[30]

Although there is atrophy of the epidermis and dermis in the aged with a reduction in barrier function of the skin, the rate of transdermal drug absorption may be diminished in elderly people owing to reduced tissue blood perfusion. This holds also true for absorption from the subcutaneous and muscular tissue. Intramuscular injections should be avoided generally in this age group because of erratic absorption e.g., antibiotics and the high risk of sterile infiltrates.[3]

**Drug distribution**

Drug distribution can be altered with age by the changing body composition and the plasma protein levels. With increasing age, the total body fat increases and the total body water decreases. These changes can alter the volume of distribution according to the lipophilicity or hydrophilicity of the drug compound. For lipophilic drugs; the volume of distribution can increase because of the up-take into the lipidic tissue along with the prolongation in the elimination half-life due to the re-diffusion of the drug from the fatty tissue,[31] and this leads to accumulation with continued use.[32] For example, the availability of vitamin D3 may be reduced because of its increased deposition in body fat compartment, which could produce relevant clinical consequences especially in post-menopausal women.[33] In addition, clinically significant differences in the volume of distribution and elimination half-life have been reported for benzodiazepines,[34] Lidocaine,[31] tricyclic antidepressants and verapamil.[35] For the more hydrophilic drugs a decrease in the volume of distribution have been described for sotalol,[31] lithium,[36] digoxin,[36,37] aspirin, non-depolarizing neuromuscular blockers and $H_2$ antagonists.[3,38] Whereas, the concentration in plasma is elevated when administered at the same dose used in young adults.[38]

Drugs in blood may be bound to plasma proteins with only the unbound fraction being pharmacologically active. Plasma albumin levels are decreased somewhat in elderly people resulting in increase in the free form of acidic drugs, whereas the concentrations of $\alpha_1$-acid glycoprotein, are increased resulting in decrease in the free form of basic drugs.[32,36] While acidic drugs bind to albumin, alkaline drugs bind to $\alpha_1$- acid glycoprotein. The degree of binding to plasma proteins is variable.[6] Certain anionic (acidic) drugs as warfarin, phenytoin, valproate, naproxen, diazepam, ceftriaxone and enalaprilat (the active metabolite of the prodrug enalapril), which preferentially bind to albumin, and cationic (basic) drugs such as lidocaine, propranolol and chlorpromazine, which bind to the $\alpha_1$-acid glycoprotein, have their free fractions in plasma modified by age.[30,31,39]

For drugs with > 90% of plasma binding, changes in plasma protein levels or competition on the binding sites with other high affinity drugs can significantly increase the free drug concentration.[40] Drugs such as warfarin, phenylbutazone, sulfonamides, phenytoin, valproate, benzodiazepines, probenecid and semi-synthetic penicillins may exaggerate the displacement of one drug by another, with potential toxic effects of the unbound form of the displaced drug, for example, warfarin causes bleeding and glipizide causes hypoglycemia.[31,32,39]

Finally, the changes of blood-brain barrier (BBB) permeability which occurs with aging might alter the pharmacokinetic of drugs acting on the central nervous system (CNS). With age, there is a decline in P-gp function which act at the BBB as an active cell membrane efflux pump for several endogenous and exogenous compounds. This could facilitate the accumulation of toxic.

**Table 1: Age-related physiological changes, their pharmacokinetic consequences and some drugs affected.**

| Physiological changes in the elderly | Pharmacokinetic consequences | Some drugs affected |
|---|---|---|
| Increased gastric pH because of decreased gastric acid secretion.<br>Delayed gastric emptying<br>Reduced splanchnic blood flow<br>Decreased absorption surface area<br>Decreased gastrointestinal mobility | Slightly decreased absorption (clinically non- significant) | Ketoprofen, indomethacin, prazocin, digoxin, ciprofloxacin, calcium, iron, vitamins, gabapentin and neucleoside derivatives. |
| Increased body fat<br>Decreased lean body mass | Increased volume of distribution and half-life of lipophilic drugs. | Vitamine $D_3$, diazepam and other benzodiazepines, lidocaine, tricyclic antidepressants and verapamil. |
| Decreased total water | Increased plasma concentration of hydrophilic drugs, and decreased volume of distribution. | Digoxin; sotalol; lithium; aspirin, and $H_2$ antagonists. |
| Decreased serum albumin | Increased free fraction in plasma of a few highly protein-bound acidic drugs. | Warfarin, diazepam, valporate, naproxen, ceftriaxone and phenytoin |
| Increased α1-acid glycoprotein | Decreased free fraction of basic drugs | Lidocaine, propranolol and chlorpromazine. |
| Decreased hepatic blood flow<br>Decreased hepatic mass | First-pass metabolism can be less effective. Phase I metabolism of some drugs might be slightly impaired. The function of CYP 3A4 is decreased with age. | Warfarin, theophylline, phenytoin, triazolam, zolpidem and 3-hydroxy-3 methylglutaryl coenzyme A (HMG COA) reductase inhibitors (atorvastatin, simvastatin, lovastatin). |
| Decreased renal blood flow and glomerular filtration rate (GFR). | Renal elimination of drugs can be impaired. | digoxin, gentamycin, lithium, Angiotensin converted enzyme (ACE) inhibitors and antithrombotics (i.e., dabigatran). |

Substances in the brain, thus increasing the risk of neurodegenerative pathology with aging.[41] Additionally, the age-related loss of P-gp-mediated BBB function may expose the brain of elderly individuals to excessive levels of drugs and xenobiotics.[42]

**Drug metabolism**

Liver metabolism has been shown to decrease with age due to liver mass decrease of 20-30% and a hepatic blood flow decline of 30-50%.[31] The effect of aging on the hepatic drug metabolism has been reviewed by various authors.[31,43] The data confirmed an increasing inter-individual variability in drug metabolism with age, but found no clear evidence that age is an individual factor of declining metabolic enzyme activity. However, declining liver blood flow rate correlates quite well with the decreased metabolism seen in elderly people.[43] Confounding factors like diet and food, frailty, smoking, co-morbidity, polypharmacy and alcohol intake are known factors contributing to the high inter-individual variability in elderly people.[43] Care should be taken when prescribing drugs to elderly patients that are metabolized by the liver and have a narrow therapeutic window (such as warfarin, theophyllines and phenytoin).[44] Significant adverse drug events (ADEs) and DDIs are most likely observed when using these drugs. A study of emergency department visits for ADEs showed that these drugs commonly require regular outpatient monitoring to prevent toxicity, as they were involved in the most unintentional overdoses.[45] The clearance of many HMG COA reductase inhibitors (atorvastatin, simvastatin, lovastatin) depends on hepatic pathway and hence metabolism slows with age. Therefore elderly patients requiring these medications often benefit from lower daily dosages.[46]

The hepatic metabolism through the cytochrome P (CYP)-450 enzyme system (Phase I reaction) decreases with aging for some drugs. Clearance typically decreases 20 to 40 % for some drugs (for example amitriptyline, nifedipine, warfarin, and verapamil), whereas that of others is unchanged. In contrast, age does not affect clearance of drugs that are metabolized by conjugation (phase II), such as paracetamol and oxazepam.[3] Many interactions occur in elderly people, the most important are probably DDIs, especially those that alter the biotransformation process.[35] The activity and expression of the major isoform, CYP3A4, is dependent on normal liver function and is progressively decreased after its optimal performance in adulthood, reflecting the relative inability of biotransformation of elderly patients.[23,36,38] On the other hand, CYP2D6, which is responsible for ~25% of drug biotransformation, is particularly resistant to the relative hepatic impairment seen in the elderly.[23,38] Clinical problems of toxicity and ADRs can be minimized or avoided when knowing the CYP

involved in the biotransformation of a given drug. In geriatric patients, several reports have shown that some drugs are poorly metabolized while others are not, although sometimes drugs from both metabolizing groups are targets of the same CYP. Anxiolytics such as triazolam, zolpidem and diazepam are all metabolized by CYT 3A4/3A5. In elderly, no impaired in metabolism occurs with diazepam while this happened with triazolam and zolpidem.[3] This indicates that there are complexity of the whole process.[23]

Pharmacogenetic variations of CYPs are expected to be age-independent. Elderly patients have an increased sensitivity to bleeding complications from warfarin, which are generally seen at lower international normalized ratio (INR) levels compared with younger patients. Pharmacogenetic variation contribute to this difference by altering both pharmacokinetics (CYP2C9) and pharmacodynamics.[47]

The different isoforms of CYP enzymes can undergo induction or inhibition, where the effect of a drug can influence the biotransformation of others. This leads to changes in the time of onset and duration of effect, pharmacokinetic tolerance, therapeutic failure and/or worsening of toxicity.[35]

The enzymatic inhibition is responsible for most drug interactions. The main drugs involved in enzyme inhibition are ketoconazole, erythromycin, nifedipine, omeprazole, progesterone, quinidine, fluconazole and fluoxetine.[39] Until now, however, no conclusive comparative data on the presence or absence of differences between the extent of enzyme inhibition or induction in the elderly and young adults was obtained.[48]

The first-pass metabolism of many drugs in the liver is reduced with aging. As a result, the serum levels of active drugs undergoing extensive first pass metabolism such as propranolol can be significantly increased.[49] On the other hand, some drugs, such as several ACE inhibitors (e.g.enalapril), are prodrugs, for which decreased first-pass metabolism may result in a decreased bioavailability.[50]

**Drug excretion**

In the elderly, the most important pharmacokinetic alteration found is the deterioration of renal excretion, a consequence of reduced GFR (1% per year of life), tubular secretion and renal blood flow, resulting in an increased t½ for all drugs that are predominantly eliminated by the kidneys and, therefore, accumulation to toxic levels and incidence of ADRs.[36] Aging of the kidney has been described to be associated with various histopathologic changes like thickening of the intrarenal vascular intima, sclerotic changes of the glomeruli and decrease in renal weight from (15-30%), as well as a parallel drop in the number of functional glomeruli and tubular secretion.[48,51,52] The renal function is known to decline as a result of several disease conditions like hypertension, vascular diseases and diabetes that are common in people over 65 years, and that might be more important than aging itself.[53] Drugs with a narrow therapeutic index like aminoglycoside antibiotics, digoxin and lithium which are likely to have serious adverse effects if they accumulate more than intended must be used carefully in elderly patients.[30] The renal clearance of ACE inhibitors and antithrombotics (i.e., dabigatran, rivaroxaban, apixaban, and edoxaban) is reduced with age. Patients receiving renally metabolized medications often benefit from lower daily doses.[46] Nonsteroidal anti-inflammatory drugs (NASIDS) can lead to decreased renal function. For drugs with narrow therapeutic ranges that are renally eliminated (e.g. digoxin) serum concentrations may need to be determined when NASIDS are prescribed on a chronic basis.[23]

**Pharmacodynamic (PD) changes in elderly people**

Pharmacodynamics (PD) affects not only therapeutic effects but also toxic and adverse effects. Pharmacodynamics (PD) depends on the concentration of the drug at the receptor, the response at receptor, postreceptor events within cells and homeostatic mechanisms. All these parts of PD may be affected with aging. The study of these changes is complicated since the effect of many drugs is also affected by reduced drug clearance in the elderly.[2] Table 2 shows some examples of PD changes in elderly people.

**Receptor properties**

In terms of PD changes, it is generally considered that enhanced sensitivity to drugs occurs with aging.[30] However, elderly people show reduced sensitivity to certain drugs.[44]

In the CNS, structural and neurochemical changes occur with aging. Due to less effective BBB, the brain may be exposed to higher drug levels in the elderly.[42] Several drugs may cause confusion in them. Antipsychotics, anticholinergics and benzodiazepines are common examples. Elderly are more susceptible to adverse effects of benzodiazepines at a given plasma level.[54] They have greater degree of sedation, impairment of psychomotor performance and higher risk of falls and fractures compared to younger peoples, so it is recommended to adjust dose in these patients.[4]

The levels of dopamine transporters, the number of dopaminergic neurons and dopamine $D_2$ receptors in the CNS decrease in elderly people,[55] leading to extrapyramidal symptoms when a certain threshold of neuronal loss is reached.[56]

**Table 2: Some examples of pharmacodynamic changes in elderly people.**

| Drug Class | Age-related Pharmacodynamic Change | Possible Clinical Consequences | Recommendation for Use in Elderly |
|---|---|---|---|
| Calcium channel blockers (CCBs)[4] | Reduced baroreceptor response to low blood pressure; Greater sino-atrial suppressive effect and less pronounced PR interval prolongation (e.g. diltiazem and verapamil). | Greater hypotensive effect potentially leading to orthostatic hypotension and falls; Decreased heart rate (e.g. diltiazem and verapamil). | Dose adjustment, especially with co medications that may lower blood pressure or decrease heart rate |
| Diuretics[4] | Reduced diuretics response due to impaired tubular secretion of the drug and decline GFR in elderly. Impaired adaptive and homeostatic mechanisms. | Reduced effectiveness of conventional doses of diuretic especially with co-prescreption of NSAIDs; increased risk of hypokalemia, hypomagnesemia, hyponatrimia (i.e. thiazide diuretics). | Careful upward-titration of drug dosage. If possible, avoid co-prescription with NSAIDs |
| B-blockers[4] | Impaired signal transduction of beta- receptor and down regulation of beta-adrenergic receptors | Reduced effectiveness of conventional doses of B-blockers. | Careful upward-titration of drug dosage |
| Antipsychotics[4] | Increased responsiveness to antipsychotics, possibly due to impaired homeostatic mechanisms and depletion of dopamine reserve in elderly people | Increased risk of anticholinergic effects such as confusion, extrapyramidal side effects, orthostatic hypotension, and cerbero- vascular adverse events | Dose adjustment; Careful assessment of need for prescribing antipsychotics; If possible, avoid co-prescription with other drugs with anticholinergic effects (e.g. tricyclics) |
| Flouroquinolones[57] | Higher sensitivity. Increased CNS toxicity as a result of age related impaired kidney function. Induce more ADRs.[57] | Adverse reactions such as confusion, weakness, loss of appetite, tremor or depression can occur in patients in old age Can cause QT interval prolongation[58] | It is recommended not to reduce the dose but to use another class of antimicrobial drug[57] |
| Antiepileptic drugs[59] | Drug sensitivity Challenge in old age because of age-related reductions in liver or kidney function[59] | Induce more adverse events. More sensitive to CNS side effects such as tremor, ataxia, and cognitive difficulty[59] | Monotherapy is recommended for antiepileptic drugs[7,59] |
| Lithium[4] | Greater sensitivity to the effects of lithium[4] | Increased risk of neurotoxic effects such as delirium, confusion, nausea, weakness, unstable gait, memory difficulties and severe anxiety[60,61] | Dose adjustment. Regular monitoring of serum lithium concentrations. This is important also when used NSAIDs, thiazide diuretics and ACE inhibitors[61] Special attention when used drugs acting on CNS such as benzodiazepines, antidepressants, antipsychotics[5] |

In line with these findings, there is an increased susceptibility to ADRs with the use of dopamnergic antagonists (e.g. antipsychotics and metoclopramide) in elderly people. These drugs can cause extrapyramidal effects including tardive dyskinesia, risk may be further increased in frail elderly people.[4,62] It is recommended to avoid these drugs in elderly.[62]

The number of cholinergic neurons and receptors, that are thought to be involved in cognitive functions, is also decreased.[3] Consequently, anticholinergic drugs such as diphenhydramine may induce delirium or increase delirium symptoms severity in elderly patients.[62,63] They can also cause confusion, worsen symptoms of prostatic hypertrophy, cause xerostomia, constipation and many other deleterious effects.[62] Diphenhydramine and other anticholinergic drugs, such as tolterodine and oxybutynin, may counteract the effects of acetylcholinesterase inhibitors used to treat Alzheimer's

disease.[23] There are strong recommendations to avoid using these drugs in elderly.[62]

Regarding anticoagulant drugs, there are an increased PD sensitivity to warfarin in elderly patients. This is due to greater inhibition of synthesis of vitamin K-dependent clotting factor at similar plasma concentrations of warfarin in elderly compared with young patients.[30] In addition, elderly are more sensitive to warfarin due to lower body weight, reductions in liver and renal function, and low dietary vitamin K intake.[64] The increased sensitivity to warfarin in the elderly has been associated with an increase in the risk for bleeding at lower INR values in elderly patients compared with younger patients.[47] Drug interactions causing small variations in serum warfarin levels may have more profound effects on anticoagulation for elderly individuals, who are also more likely to experience drug interactions due to polypharmacy.[65]

Lower doses of warfarin are recommended for elderly patients; if possible avoid co-prescription with drugs which may potentiate anticoagulant effect of warfarin (examples aspirin, amiodarone, quinidine, phenytoin, ciprofloxacin, allopurinol, cotrimazole, erythromycin, fluconazole, thyroxine, trimethoprim-sulfamethoxazole etc.[4]

The concomitant use of warfarin with antiplatelet agents including prescription and non-prescription NSAIDs and clopidogrel can increase bleeding risk without increasing the INR.[66] Physicians, pharmacists and nurses must consult elderly patients regarding the potential adverse consequences due to other medications or alternative therapies used with warfarin. They must also encourage adherence to regular INR monitoring.[67]

Pharmacodynamic sensitivity to beta-adrenergic agents declines with age.[4] A reduction in response to beta-adrenoreceptors agonists has been reported for elderly people.[3] With increasing sympathetic activity with age, beta-adrenoreceptors are downregulated by increased serum noradrenaline levels.[3,4] The use of beta-adrenoreceptors blockers has therefore been questioned and proven to be less effective in elderly people compared to young adults.[68] The ability of the cells to respond to receptor occupation (e.g. signal transduction) can influence the magnitude of a drug effect.[3] The age-related changes in response to beta-adrenergic agents may be also the result of impaired signal transduction of beta-receptor in elderly due to decrease in Gs proteins interactions.[4,69]

**Homeostatic mechanisms**

A progressive reduction in homeostatic mechanisms is one of the fundamental characteristics of aging. Hence, following a pharmacological perturbation of a physiological function, more time is required to regain the original steady-state as counter regulatory measures are reduced. Therefore, drug effects are attenuated less in elderly people, the reactions may be stronger than in young individuals and the incidence of adverse drug effects is higher, despite the general decline in receptor number or responsiveness.[3] A typical example for the consequences of the decrease in homeostatic mechanisms is the increased susceptibility of elderly patients to postural hypotension in response to drugs that lower the arterial blood pressure.[48] As an example, consider the antihypertensive drug prazosin. This peripheral [alpha]-adrenergic receptor blocker effectively reduces blood pressure in most patients. A common adverse effect of prazosin in many elderly patients is first-dose syncope. Because the aging process can affect the ability of the body to recover from orthostatic changes, [alpha]-blockers are commonly associated with orthostatic hypotension and for that they must be taken with extreme caution in elderly people.[70] Some antipsychotic medications block $\alpha_1$-adrenergic receptors, augmenting the effects of antihypertensive medications or causing untoward orthostatic hypotension that could be responsible for an elderly person falling.[23]

There is also a decline in electrolyte homeostatic mechanisms with aging.[71] The ability to cope with sudden changes in electrolyte levels is reduced. Elderly patients have a greater susceptibility to adverse drug effects, for example, hyperkalaemia or hyponatremia. Such adverse effects are quite common.[2] The common occurrence of dysregulation of the baroceptor reflexes in elderly patients frequently causes an increased sensitivity to the blood volume depletion induced by diuretics.[72] A reduced PD response in diuretics does not mean greater safety, because of the correct use of these drugs should always taken into account the potential risk of orthostatic hypotension and falls.[72]

## CONCLUSION

The word aging is often used to only mean senescence. The number of elderly people is increasing in most of the world. Many biological changes occur with ageing such as; decrease in physiological fitness, reduction of homeostatic capabilities and decline in functional reserves. The physiological and functional capacities of the body in elderly might alter the PK and PD of drugs leading to ADRs. Chronic diseases, morbidity, co morbidity, life style (smoking), genetic and environmental factors can also impact the pharmacological effect of drugs. Polypharmacy can modify PK and PD effects of drugs due to DDIs which can be PK or PD. The age-related physiological changes that affect the PK profile can occur during drug absorption, metabolism, distribution and elimination. Age-related changes in PD may occur at the receptor or signal-transduction level, or homeostatic mechanisms may be attenuated. The study of PD changes is complicated since the effect of many drugs is also affected by reduced drug clearance in the elderly. Pharmacokinetic PK and/or PD changes in elderly people may account for either the toxic or sub therapeutic response that often occurs in this population. Some

general recommendations can be taken into account for appropriate drug prescribing. First, special caution should be taken when prescribing drugs to elderly patients notably drugs with narrow therapeutic window. These drugs commonly require regular monitoring to prevent overdose, toxicity and DDIs. Second, physicians must be familiar with PK and PD changes for drugs prescribed to the elderly, and DDIs must be anticipated. Third, dose should be adjusted for some drugs. For others, careful upwards titration of drug dosage is needed. Fourth, some drugs must be avoided in elderly. The benefit/risk profile of every prescribed medication should be frequently reassessed. Fifth, physicians, pharmacists and nurses must consult elderly patients regarding the potential adverse consequences of drugs when using alone or together with other medications. Finally, It is important to have better understanding of the effects of aging on PK and PD of drugs. New researches must be conducted to reach optimal drug use, and guidelines for the using of drugs in elderly must be put and followed up.

## CONFLICTS OF INTEREST

The authors have no conflicts of interest that are relevant to the content of this paper.

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