Pharmacokinetic and Pharmacodynamic Considerations in Elderly Population

Jatinder Kaur Mukker, Ravi Shankar Prasad Singh and Hartmut Derendorf

Abstract Physiological changes with age may alter absorption, distribution, metabolism, and excretion of drugs in the elderly population. Reduced elimination and prolonged half-life are most commonly observed pharmacokinetic changes in older patients whereas altered sensitivity to drugs and change in receptor affinity are major pharmacodynamic changes. These potential changes should be considered in designing dosage regimen to elderly population during clinical and pharmaceutical development as well as prescription. Understanding and managing these age-related pharmacokinetic and pharmacodynamics changes is an important factor for the benefit to risk ratio of a new drug product. The physiological changes affecting pharmacokinetics and Pharmacodynamics of drugs and their clinical implications are discussed here.

Keywords Pharmacokinetics · Pharmacodynamics · Elderly · Age-dependency · Geriatrics

Introduction

Elderly people who are 65 years of age or older is the fastest growing drug consumer population in the United States (US). According to US Department of Health and Human Services, population age 65 years or older numbered 45 million in 2013 which is an increase of 25 % since 2003 [1]. About every one in seven Americans is an older adult. The definition of older or elderly adult is arbitrary; however from clinical pharmacology perspective, individuals of 65 years or older are considered 'elderly population'. Elderly population contributes to approximately 26 % of the drug expenditures in US [2].

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The pharmacology and pharmacokinetics of a drug in the elderly population may be very different than in the adult below 65 years of age. Age related changes in physiology, chronic disease conditions, and poly-pharmacy may make elderly people to respond differently than expected [3, 4]. Not only the frequency, also severity of adverse effects increases with age, which is the most common cause of hospitalizations and high drug expenditure in case of elderly population. In 2013, patients 65 years of age or older represented 40 % of hospitalized adults [2].

Altered drug response in elderly population is mostly suggested due to changes in drug pharmacokinetics and pharmacodynamics with age [4]. Major pharmacokinetic changes include decrease in drug clearance with age which may lead to greater drug exposure and prolonged half-life in elderly population compared to healthy young adult [5]. Major pharmacodynamic changes include altered drug sensitivity (greater or lesser) especially in central nervous system (CNS) and cardiovascular (CVD) drugs [4], and these changes in drug sensitivity may lead to altered drug response and may potentiate adverse drug effects.

In this chapter, changes in pharmacokinetics and pharmacodynamics with age and its impact on pharmacotherapy in elderly population will be discussed.

Pharmacokinetic Considerations in Elderly Population

Absorption

Absorption of drugs usually remains unchanged in healthy elderly population although changes are reported in gastrointestinal physiology with age. Conceptually, gastric pH increases with age and capacity to secrete gastric acid decreases [3, 6]. Elevated gastric pH and reduced acidity may affect the ionization and solubility of drugs. Altered ionization and solubility of drug molecules will impact the permeability and thus absorption across gastrointestinal membranes [7]. Gastric motility gets reduced with age which leads to faster stomach emptiness [8]. Reduced gastric surface area and lower gastrointestinal blood flow with age also contributes to reduced absorption of drugs across gastrointestinal membranes [9, 10]. In elderly population, tissue perfusion is slower compared to young adults. This may affect the absorption of drugs administered by subcutaneous, intramuscular and transdermal route [3]. Theoretically, all these physiological changes with age may impact the absorption of drugs in elderly; however clinical implications of these changes are not very apparent.

Although drug absorption remains relatively unchanged in healthy elderly population, certain disease conditions and administration of concomitant medications may alter the specific drug absorption in elderly. Use of anticholinergic drugs reduces saliva secretion and impedes the rate but not the extent of drug absorption by oral mucosa, e.g., buccal midazolam and sublingual nitrates [3]. Reduction in gastrointestinal transporter mechanisms with age can decrease the absorption of

vitamin B_{12} and iron [6]. Conversely, prokinetic agents, such as erythromycin and domperidone may increase the rate of absorption of orally delivered drugs [3, 6].

Distribution

Distribution of lipid soluble drugs increases and water soluble drugs decreases in elderly population. As people age, there is reduction in total body water content and muscle mass and increase in content of body fat [4, 11, 12]. These changes affect the volume of distribution (V_d) of drugs in elderly population. Low body water content leads to lower V_d for water soluble drugs and high body fat contributes to higher V_d for lipid soluble drugs [10]. Since volume of distribution is a proportionality constant between plasma concentration (C_p) and dose of the drug, C_p will be different for water and lipid soluble drugs as age progresses compared to healthy adult when same dose will be prescribed to old and young adult. Lipophilic drugs will have higher V_d and prolonged half-life in elderly [5]. Diazepam is a lipid soluble drug and has two fold higher volume of distribution in elderly population. If the same dose as that of young adult will be administered to elderly person, it could prolong its half-life by two folds in elderly person [13]. Thus 50 % of adult dose is generally recommended in elderly populations. Conversely, V_d decreases for hydrophilic drugs and equal doses as in young individuals would results in higher plasma C_p of drugs. Major examples include aspirin, famotidine, and tubocurarine [10, 14]. Additionally, reduced cardiac output, decreased renal and hepatic blood flow, and increased peripheral vascular resistance in elderly population significantly affect distribution of drugs [3].

Plasma protein binding does not change significantly in healthy elderly individuals. Most of drugs bind to plasma proteins such as albumin and α-acid glycoprotein, when circulating in the blood. In general, acidic drugs bind to albumin and basic drugs bind to α-acid glycoprotein [15]. Binding of drugs to plasma proteins leads to change in free fraction of drugs, which is primarily responsible for the therapeutic action. Age does not contribute much to change in plasma protein levels [4]. Thus in healthy elderly population, free fraction of drugs changes minimally to exhibit their therapeutic actions.

Although in healthy elderly population, there is minimal change in plasma protein levels; chronic illnesses may cause alteration in their plasma protein levels. In frail and hospitalized elderly person, serum albumin levels can be significantly reduced, leading to low plasma protein binding and higher free fraction of the administered drugs. Most common drugs whose plasma protein binding is decreased include sodium valproate [16] and warfarin [17]. High free plasma levels of drugs may increase the potential of drug toxicity, adverse effects and drug-drug interactions. Similar to albumin, binding of lipophilic drugs to α-acid glycoprotein increases with acute illness such as myocardial infarction. For example, propranolol and lignocaine may bind to α-acid glycoprotein to a greater extent and lead to decrease in its free fraction in plasma [18, 19]. However, higher binding to α-acid

glycoprotein is temporary and goes away as elderly people recover from acute illness [20].

In addition, gender is also known to be a determining factor of plasma protein binding of drugs in elderly patients. Harry et al. reported 50 % decrease in total plasma clearance of alfentanil in elderly women compared to men, and these differences are believed to be due to difference in alfentanil's plasma protein binding in both genders in elderly population [4, 21]. Since alfentanil is an intermediate extraction ratio drug, liver blood flow or intrinsic clearance could not explain the large differences (50 %) in total plasma clearance in women.

Metabolism

Metabolic ability of the liver declines with age and affects significantly Phase-I enzyme metabolism compared to Phase-II enzyme metabolism [3]. Number of structural and functional changes occurs in liver with age that can impact the metabolism of the drugs including decline in hepatic mass (30 %) and perfusion rate (40 %) of the liver [22, 23]. These changes lower the metabolic elimination of drugs and leads to prolonged half-life of drugs. Phase-I metabolizing enzymes (oxidation, reduction, and hydrolysis) such as microsomal mixed function oxidases are more affected than the Phase-II conjugating enzymes such as glutathione transferase and UDP glucuronyltransferase [4]. However, literature also report inconsistency between age and Phase-I enzymatic reactions. No consistent relationship was found between age and the activity of various microsomal cytochrome P450 (CYPs) in in vitro system [24]. Schmucker et al. [25] also reported no significant age dependent differences in activity of mixed functional oxidases using an in vitro enzymatic setup.

Contradictory evidences in age dependent changes in hepatic enzymes activities in elderly can be attributed to multiple factors. First, inter-individual variability increases with age [26]. Second, in vitro experimental result may not always be reflective of clinical observations. For example, clinical studies suggest decrease in metabolic clearances (20–40 %) with age for theophylline [27] and imipramine [28] but in vitro experiments show no changes in metabolic clearances using mixed functional oxidase systems [25].

Clinical studies suggest altered metabolic clearances of many drugs in elderly population. In elderly patients, demethylation of desipramine is slower, which leads to reduced clearance and prolonged elimination half-life [29, 30]. Similarly, decarboxylation of levodopa is a major metabolic pathway in its first pass metabolism and the enzyme responsible for decarboxylation decreases with age. In a clinical study, area under the curve (AUC) of levodopa was 54 % greater in elderly subjects compared to young subjects [31]. Other drugs including verapamil, amitriptyline, and morphine also have higher bioavailability in elderly subjects than in young adults [32, 33].

Higher bioavailability and reduced metabolic clearance in elderly population may necessitate dose adjustment to avoid any adverse events. The use of

antihypertensive agents (with high extraction ratio) in elderly are associated with hypotension as a potential adverse effect if dose normalization is not done in elderly population. Reduced metabolic clearance with age leads to higher bioavailability and prolonged actions in antihypertensive therapy and subsequently causes hypotension in elderly population [4]. Therefore, dose and administration time normalization should be considered before starting antihypertensive therapy in elderly population. For example, ramipril (antihypertensive drug) is administered as 1.25 mg (initial dose) to elderly compared to 2.5 mg (initial dose) to young adults and gradual dose titrations are performed due to higher risk of hypotension as adverse reactions in elderly population [34–36].

Increase in enzyme induction with age may lead to higher metabolic clearance and affect therapeutic outcomes of drugs. Enzyme induction usually takes longer time to occur and may causes therapeutic failure if drug is to be administered for multiple days. For example, decline in antipyrine clearance is reported with time in elderly individuals who smoke [37]. It is suggested that smoking may have induced the microsomal enzyme activity. However, role of enzyme induction in therapeutic effects of the drugs in elderly is still controversial. For example, rifampicin is a known potent inducer of microsomal activity but failed to have any induction effects on elimination half-life of antipyrine [38].

Excretion

Major changes occur in renal size, function and perfusion with age causing decreased renal clearance of drugs. Glomerular filtration rate (GFR) and renal plasma flow (RPF) gradually declines with age. There is a greater decrease in RPF ($\sim$50 %) than GFR, causing significant increase in filtration fraction in elderly population [39]. In renal physiology, filtration fraction is the ratio of GFR to RPF. In addition, diminished reabsorbing capacity and loss of tubular function is also observed in elderly population [40]. All these factors may lead to reduced overall renal elimination of administered drugs.

Other factors including coexisting medical conditions, poly-pharmacy, and increased inter-individual variability with age can significantly impact the renal clearance of the drugs [3]. A population pharmacokinetic model predicts high risk of digoxin toxicity if the same adult dose is administered to elderly population with co-existing medical conditions as renal impairment and heart failure [41]. The study analysis suggested a limited daily dose to 0.125 mg or less per day and reported significant reduction in digoxin clearance (43 %) with covariates such as body weight, congestive heart failure, and concomitant use of medications such as calcium channel blockers, spironolactone, etc. [41]. Non-steroidal anti-inflammatory drugs (NSAIDs) use causes renal adverse effects in elderly population such as acute kidney injury, acute interstitial nephritis, proteinuria and acute tubular necrosis [42]. Concomitant use of diuretics and other hypertensive medicines with NSAIDs potentiates these adverse effects [43–47].

Measuring endogenous creatinine levels is a better way to assess renal function in elderly population. Serum creatinine is the most common evaluation used to test renal functions; however, changes in body muscle mass with age make this evaluation misleading. Corsonello et al. [48] reported that 50 % of elderly people with normal serum creatinine have reduced GFR. Measurement of endogenous creatinine clearance would be a more precise way to assess renal function and is helpful to adjust dose of renally excreted drugs. However, compromised tubular secretion of creatinine with age may lead to altered GFR and need to be considered while selecting and adjusting the dose in elderly population. Additionally, GFR should be estimated using well established formulas such as Cockcroft and Gault [49] and modification of diet in renal diseases [50].

Figure 1 represents major pharmacokinetic changes with age including changes in absorption, distribution, metabolism, and excretion. Pharmacokinetic changes with age may increase the potential of adverse effects or sub therapeutic plasma levels of drugs, if dose normalization is not done in elderly population. Therefore, above-mentioned important factors need to be evaluated during the drug development phase to provide accurate information for prescribing the drugs to the older patients.

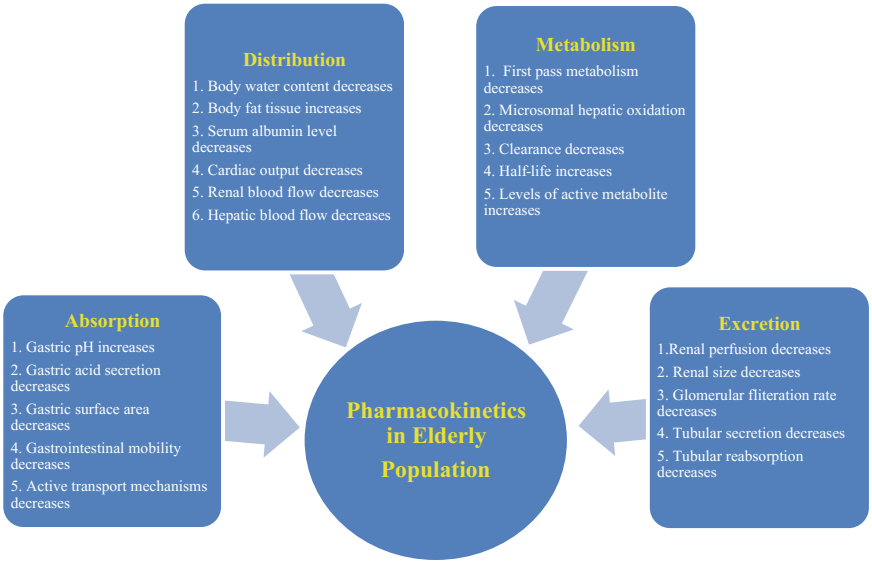

Fig. 1 Diagrammatic representation of major pharmacokinetic changes (changes in absorption, distribution, metabolism, and excretion) in elderly population

Pharmacodynamic Considerations in Elderly Population

Pharmacodynamic changes are less studied and known compared to pharmacokinetic changes. It is relatively easy to understand the change in pharmacokinetics by measuring blood/biometrics drug concentrations over time; however, it is difficult to measure the drug response due to number of reasons. First, it is very challenging to develop and validate appropriate measures of drug response especially at the site of action. Pharmacodynamic changes may occur at variety of sites in the body using various drug-receptor interfaces and through number of mechanisms. Most of the time, it is difficult to measure drug response at site of action especially when the mechanism of action is not known. Second, pharmacodynamic response depends on receptor number and affinity, signal transduction mechanisms, cellular responses, and homeostatic mechanisms along with inter-individual variability [4]. Thus, it is difficult to understand and measure the complex cascade of events between drug administration and drug response. Third, human body is a complex system and it is difficult to investigate abnormality with a good precision. It is possible to conduct in vitro and animal experiments to differentiate and address various scientific issues between receptors and/or post receptor changes (second messenger mechanisms); however, extrapolation from animal data to human data further complicates the situation [4, 51].

In general, pharmacodynamic response declines with age and may be explained by number of factors. These factors include changes in receptor number and affinity [52], changes in CNS [53], changes in reflux responses [54], and alterations in fluid and electrolyte balance [55]. In the following paragraphs, we will discuss these factors in details.

Generally, age causes change in receptor density, affinity, and the ability to activate second messengers in signal cascades impacting the pharmacodynamics response in elderly population. Lippa et al. [56] observed cholinergic dysfunction and memory loss in aged rats due to decreased number of muscarinic acetylcholine receptors with aging. With age, decrease in number of μ opioid receptors, as well as, decrease in opioid peptide content is reported. Specific drugs binding to these receptors lead to increased impotence, hypodipsia, anorexia like behavioral changes in elderly population [57, 58]. Age causes diminished calcium responsiveness and changes in calcium mobilization, which is required for different functions including secretion, neurotransmission, muscle contraction, and cell division. Thus diminished calcium responsiveness could affect all these processes requiring calcium [4, 59].

The sensitivity of CNS acting drugs get altered with age, e.g., benzodiazepines, tricyclic antidepressants, barbiturates, opiates etc. Albrecht et al. suggested 50 % reduction of dose of midazolam in elderly population to obtain comparable pharmacodynamic outcomes to that in young adults. Significant reduction in the half maximal effective concentration (EC_{50}) was observed in elderly population due to increased sensitivity of midazolam in older patients [60]. Besides age, blood supply to the brain may get compromised by atherosclerotic narrowing of vertebral and

carotid systems in elderly population. Decrease in blood supply could lead to neuronal loss and altered drug sensitivity [4].

Sensitivity to anticoagulant drugs also increases with age. Although there were no significant age dependent pharmacokinetic differences reported in case of warfarin, increased effect, and risk of bleeding is reported in elderly subjects when same dose of warfarin is administered to elderly and young adults likely due to increased intrinsic sensitivity of warfarin with age [17]. Therefore, lower initial and standard doses are recommended in elderly patients. Similarly, increased sensitivity to anticoagulant effects of dabigatran was observed in elderly patients, and lower doses of dabigatran are recommended in patients 80 years of age or above [61].

Elderly population is less sensitive to baroreceptor reflex and responsiveness. Because of these changes, they are more prone to postural hypotension and bradycardia when they take nitroglycerin, diuretics, phenothiazines, and peripheral α-blockers [54]. It is suggested that these symptoms are due to increased vascular smooth muscle action of nitrates.

In conclusion the pharmacodynamics changes occurring with age have to be considered in development and prescription. This might not only relate to the prescribed dose but also to the risk-benefit assessment of specific drugs for older patients due to the declining homeostasis, increasing vulnerability and adverse drug reactions severity. For example, the increased risk for hypotension with antihypertensive drugs or the increased sensitivity for CNS drugs increases the risk for falls, which are a major factor for mobility loss [62].

Population Pharmacokinetics/Pharmacodynamics (PK/PD): Dose Selection and Regimen in Elderly Population

Population PK/PD modeling approach enables to account inter-individual variability by identification of covariates and to correlate the drug concentration with drug response in a modeling framework to allow prediction of concentrations and response in individuals in whom the drug has not been tested [63]. PK/PD approach uses a mathematical relationship to relate dose to plasma concentration and subsequently plasma concentration is related with pharmacodynamic response. Population PK/PD is not only able to determine the population parameters and covariate effects (fixed effects) but also estimate inter- and intra-individual variabilities (random effects) in the population. These covariates may include intrinsic and extrinsic patient related factors such as body weight, age, sex, renal and hepatic functions, genetic markers, biological markers etc. and non-patient related covariates [64]. Estimation of parameters and identification of the right set of covariate relationship in PK/PD modeling framework allows prediction of

concentration and response; therefore, enables design of individualized dosing regimen. Mostly, these models are used for the dosing regimen design in the population in which the model has been developed. In certain situations (based on reasonable assumptions), these models may be used for dosing regimen design in other special populations in which the availability of the data is very limited due to practical and ethical considerations [65]. Most examples include extrapolation of the model into pediatric population, pregnant women population, where the data is very limited; however, similar approach may be applied for geriatric population, wherever applicable.

In geriatric population the pharmacokinetics, efficacy and safety data is still very limited and therefore, the PK/PD modeling framework developed for young adult population may be used for the prediction of the dosing regimen in elderly patients. Ideally, the drug should be studied in geriatric population owing to the physiological changes those could affect pharmacokinetics and pharmacodynamic response in elderly patients. Taking into account the recent update of the ICH E7 guideline it can be expected that more studies including relevant older patient populations in clinical trials will become available [66, 67].

Saeed et al. [68] proposed a framework for PK/PD modeling and simulations in elderly populations for prediction of dosing regimen (Fig. 2). This framework describes the scenario when clinical safety, efficacy, pharmacokinetics, and population pharmacokinetics studies in elderly population is needed and the scenario when this can be avoided. In most cases, a combination of safety, efficacy, pharmacokinetics, and population pharmacokinetic studies are needed for appropriate dosing regimen design. In a case the indication, disease stage, pathophysiology, dose-response relationship, treatment outcome and PK/PD relationship is similar to young adults, a modeling and simulation approach can be used for dosing predictions in elderly population. Elderly patients are seldom included in most of the pharmacokinetic, safety, and efficacy studies; however, more studies on elderly population is needed to understand the differences in pharmacokinetic and pharmacodynamics in elderly patients [67].

Given that most elderly patients use multiple drugs, the prediction of drug-drug interaction (DDI) is challenging. The study of all possible combination of drugs used in elderly population is difficult. However, a new and emerging physiology-based pharmacokinetic (PBPK) approach may be used for DDI predictions in elderly populations [69]. PBPK is currently being extensively used for drug-drug interaction predictions in young adults, children, and pregnant women [70]; however, it has not been used extensively in elderly population. PBPK can incorporate the physiological differences from young adults into the model to predict the pharmacokinetics of drugs in elderly population.

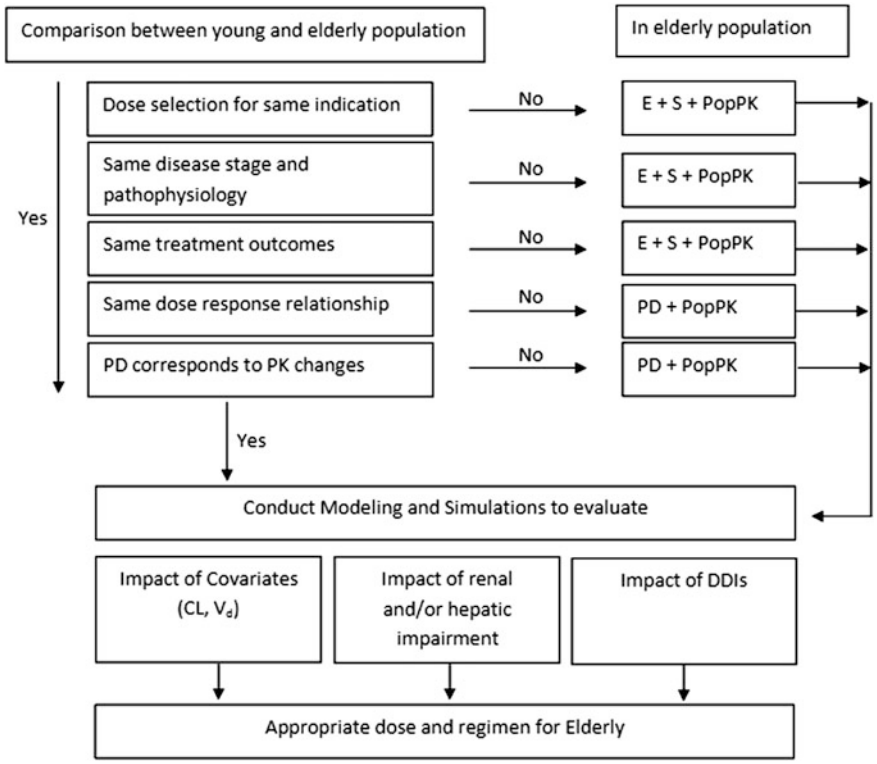

Fig. 2 Proposed framework for pharmacokinetic/pharmacodynamic (PK/PD) modeling and simulations in appropriate dose and regimen recommendations for elderly population. This framework describes need for clinical safety (S), efficacy (E), pharmacokinetics (PK), and population pharmacokinetics (PopPK) studies or utility of modeling and simulations in elderly population based on comparison between young and elderly population [63]

Conclusion

Pharmacokinetic and pharmacodynamic considerations are important for dosage recommendations in elderly population. Physiological changes with age are well known but their impact on pharmacokinetics and pharmacodynamics of drugs are less studied and less understood in elderly patients, and this limited knowledge often poses challenges in dosing elderly patients. Furthermore, the prevalent practice of poly-pharmacy in elderly patients complicates the dosing recommendations in elderly patients. Therefore, more pharmacokinetic and pharmacodynamic studies are required in elderly patients to assess the benefits/risks of administered drugs. Newer approaches such as population PK/PD and PBPK approaches may be used in designing dosing regimen and estimate the risk-benefit of drugs in elderly patients.

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