

Geriatric clinical pharmacology and clinical trials in the elderly

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The aging process is linked to changes in the physiological function of organs and changes in body composition that alter the pharmacokinetics of drugs and pharmacodynamic responses. Comorbidity and polypharmacy in the elderly decreases tolerability of drugs, leading to greater vulnerability to adverse drug reactions than that observed in younger adults. In geriatric pharmacotherapy, the general recommendation is dose reduction and slow titration, which is based on pharmacokinetic considerations and concern for adverse drug reactions, rather than clinical trial data. Older patients are under-represented in clinical trials. In the absence of evidence, extrapolation of risk-benefit ratios from younger adults to geriatric populations is not necessarily valid. Sound evidence through prospective clinical trials is essential, and geriatric societies, governments, and patient advocacy groups should collaborate to promote the inclusion of older people in clinical trials. It is believed that all involved in clinical trials have both an obligation and an opportunity to eliminate age discrimination in clinical trial practice.

Introduction

The most important and common medical intervention in the elderly is drug therapy. Due to unprecedented increases in the proportion of elderly people in a population, an understanding of geriatric pharmacology has become very important for drug therapy in elderly patients. In addition to drug treatment itself for medical problems caused by aging, such as dementia and degenerative diseases, elderly patients experience many treatment-related problems compared with younger patients. Examples of such problems include reduction in physiological function, change in pharmacokinetics/pharmacodynamics, and vulnerability to adverse drug reactions, polypharmacy, drug interactions, and low compliance. Understanding the various factors that affect drug treatment outcomes in the elderly requires knowledge of basic and clinical pharmacology of geriatrics. Using this knowledge, attention should be applied to providing appropriate drug therapy.[1]

Organ function is reduced and body composition is altered with age. The pharmacokinetic processes of absorption, distribution, metabolism, and excretion differ compared with young

adults. Moreover, the elderly have greater risk of disease because of the aging process, which is accompanied by multiple chronic conditions. Drug tolerability decreases, while patients are often exposed to multiple drugs. Therefore, elderly patients are much more vulnerable to adverse drug reactions than younger adults. The fifth most common cause of hospitalization in elderly patients is related to drug use, and accounts for approximately 20% of hospitalizations.[2] Concomitant use of more than 5 drugs (polypharmacy) is observed in 20 to 40% of elderly patients.[3] Thus, the risk of adverse drug events due to drug-drug interactions is high. In addition, it is common to administer new drugs to elderly patients for the relief of an atypical symptom without appropriate evaluations; this causes new drug-induced side effects and perpetuates a vicious circle.

Prescribing for geriatric patients requires an understanding of the efficacy of medication in older people, an assessment of the risk of adverse drug events, and a decision about the dosage regimen and careful monitoring of the patient's response. This requires an evaluation of evidence through clinical trials. Given that most diseases occur in older people, and that this patient group is the major recipients of drug therapy, more research and a better evidence base through clinical trials is essential to guide clinicians who manage geriatric patients.[4] Patients older than 65 years are not well represented in clinical trials,[5] and this under-representation impacts the care of elderly patients.[6]

The elderly population in Korea has increased rapidly. In 2011, the proportion of the population aged over 65 was 12.2%.[7] Similarly, medical expenses of the elderly have increased exponentially and accounted for 33.3% of the total medical costs for Korea in 2012.[8] New drugs and treatments that have undergone evaluation during clinical trials will provide great benefit to the elderly. However, the participation of elderly patients in clinical trials is not usually favored; therefore, there is a lack of evidence for optimum therapy for elderly patients, especially in the cases of comorbidity and polypharmacy. The regulatory agencies of Europe and the United States have been aware of the relevance of obtaining information concerning the efficacy and safety of new drugs in the elderly since the late 1980s. In 1994, the International Conference of Harmonization (ICH E7) guidance on studies in support of geriatric population clearly stated that age should not be a barrier to participation in clinical trials.[9] The guidance states that “There is no good basis for the exclusion of patients on the basis of advanced age alone, or because of the presence of any concomitant illness or medication, unless there is reason to believe that the concomitant illness or medication will endanger the patient or lead to confusion in interpreting the results of the study. Attempts should be made to include patients over 75 years of age and those with concomitant illness and treatments.”[9] According to this guidance, separate pharmacokinetic and pharmacodynamic studies of older populations may be needed, particularly when assessing drugs that target the central nervous system, which implies special consideration of geriatric pharmacology is necessary.

Good understanding of geriatric clinical pharmacology is essential for appropriate patient care and clinical trials in the elderly. This article presents a brief review of principles of geriatric clinical pharmacology and discusses the challenges and opportunities to participation of the elderly in clinical trials.

Clinical pharmacology of the elderly

Pharmacokinetics

All aspects of pharmacokinetics are affected by aging. The change in absorption is often not a major clinical problem, but significant changes can be observed in distribution, metabo-

lism, and excretion of drugs. Decreased drug clearance is an obvious finding because of reduced renal excretion and hepatic metabolism in older adults. These pharmacokinetic differences can be the basis for predicting the safety and efficacy of drugs commonly used in the elderly. All aspects of pharmacokinetics are affected by aging (Table 1).

Evidence of the effects of aging on pharmacokinetic parameters can be generated with a dedicated clinical pharmacokinetic study or population pharmacokinetic data analysis. For drugs that will be mainly used by elderly patients, a dedicated pharmacokinetic study in elderly subjects is usually required for a new drug application according to ICH E7 guidelines. If possible, a population pharmacokinetic approach can be applied by obtaining a small number of samples per patients in late-phase clinical trials, followed by an attempt to explore the effects of aging on pharmacokinetics through pharmaco-statistical modeling analysis.[9]

Absorption

Aging can cause changes in the absorption process of the drug. Gastric acid secretion decreases, intragastric pH increases, gastric emptying time is delayed because of decreased motility of the gastrointestinal tract, and blood flow in the gastrointestinal tract is reduced.[4] Such changes may not significantly affect the extent of drug absorption, and rarely lead to clinically significant changes in the drug absorption process. One exception is levodopa, which requires particular attention because its absorption may increase due to a reduction in dopa-decarboxylase in the gastrointestinal mucosa causing an increase in drug levels in the blood.[10]

Distribution

Changes in body composition in older adults are characterized by a progressive reduction in total body water and lean body mass, resulting in a relative increase in body fat.[11] This change can affect the volume of distribution (Vd) of the drug. For lipid-soluble drugs, such as diazepam and thiopentone, Vd increases, leading to prolonged half-life and duration of action. In the case of water-soluble polar drugs, such as digoxin and theophylline, there is an initial rapid elevation in plasma concentration fol-

Table 1. Pharmacokinetic changes in the elderly

Process	Change	Clinical Significance
Absorption	Generally unchanged	Little
Distribution (Vd)	↑Hydrophobic drug ↓Hydrophilic drug ↓Albumin	↑T _{1/2} ↑Plasma Concentration ↑Free Drug Concentration
Metabolism	↓Hepatic Blood Flow ↓Liver mass	↑T _{1/2}
Excretion	↓Glomerular filtration rate	↑T _{1/2}

T_{1/2} = elimination half-life; Vd = volume of distribution; ↑ = increase; ↓ = decrease

lowing drug administration due to decreased Vd.[12]

In addition, protein binding of drug decreases and free fraction increases in the elderly. Such changes may be marked with acidic drugs, such as cimetidine and furosemide.[13] However, clinical relevance is probably limited in most cases because the initial and transient effect of protein binding on free plasma concentration is rapidly counterbalanced by its effects on clearance.[14]

Metabolism

Studies on human liver tissue showed that cytochrome (CYP) P450 enzyme activity is maintained even with advanced age.[15] These results were confirmed by in vivo studies for CYP3A activity.[16] Aging is associated with a 40% reduction in hepatic blood flow and 30% reduction in liver mass.[1] Because the activity of drug metabolizing enzymes is preserved, impaired hepatic drug clearance in older people is probably represented by age-related changes in liver size and hepatic blood flow.[17]

Orally administered drugs with large flow-dependent first-pass effects (e.g., labetalol, propranolol, verapamil, and morphine) should be used with caution because the reduction in hepatic blood flow could lower the first-pass effect and increase drug concentrations in the elderly.

Excretion

It is well known that renal function progressively decreases with increasing age, and when accompanied by a chronic disease, the decrease in function is further accelerated. However, serum creatinine concentration in older adults is not high enough to accurately reflect renal function because of significantly reduced muscle mass.[18] Calculating creatinine clearance as a standard indicator of glomerular filtration should be conducted to estimate renal function. In the case of drugs mainly excreted via kidney, appropriate dose adjustments should be made for older patients.

Pharmacodynamics

The action of a drug is derived from its interaction with its target receptor leading to apparent drug responses. Aging is associated with changes in pharmacodynamics and ability to maintain homeostasis in the body. A well-known example is the reduced reactivity of β -adrenergic receptors in the elderly. The affinity and number of β -adrenergic receptors are reduced,[19] and it is thought to be due to changes in the signal transduction system downstream of receptor binding. In contrast, the sensitivity of neuropsychiatric drugs, including benzodiazepine, is generally increased in the elderly, resulting in psychomotor dysfunction at lower doses than in younger adults.[20] It is often difficult to make generalizations because the effect of age on drug sensitivity varies with the drug studied and the response measured. Some important age-related changes in pharmacodynamics are illustrated in Table 2.

The homeostatic response provides important information to

Table 2. Selected pharmacodynamic changes in the elderly (quoted from Ref. 12)

Drug	Pharmacodynamic effect	Age-related change
Adenosine	Heart-rate response	↔
Diazepam	Sedation, postural sway	↑
Diltiazem	Antihypertensive effect	↑
	Acute PR interval prolongation	↓
Diphenhydramine	Postural sway	↔
Enalapril	ACE inhibition	↔
Furosemide	Peak diuretic response	↓
Heparin	Anticoagulant effect	↔
Isoproterenol	Chronotropic effect	↓
Morphine	Analgesic effect	↑
	Respiratory depression	↔
Phenylephrine	Alpha1-adrenergic responsiveness	↔
Propranolol	Antagonism of chronotropic effects of isoproterenol	↓
Scopolamine	Cognitive function	↓
Temazepam	Postural sway	↑
Verapamil	Acute antihypertensive effect	↑
Warfarin	Anticoagulant effect	↑

↑ = increase; ↓ = decrease; ↔ = no significant change

explain the overall reaction of the body to a drug. In the elderly, homeostatic regulation of the body is reduced. For example, mean blood pressure is increased, but the occurrence of orthostatic hypotension increases significantly. Two-hour postprandial blood glucose levels increase by about 1 mg/dL every year after 50 years of age. Temperature control function also decreases, which explains why older adults are less likely to withstand cold environments.[21]

Adverse drug reactions and drug interactions

Aging brings about changes in pharmacokinetic and pharmacodynamic processes; thus, drug-related adverse effects occur frequently in the elderly. In addition, the elderly tend to have multiple chronic diseases requiring polypharmacy leading to undesirable drug interactions. Risk of drug-related adverse effects increases exponentially with the number of drugs used. To date, studies that investigate drug-drug interactions in the elderly population are rarely conducted. Inhibition of drug metabolism by other drugs does not appear to be altered with age. For example, ciprofloxacin and cimetidine suppress the metabolism of theophylline by about 30% in both healthy elderly and young adults. The effects of aging on the induction of drug metabolism are diverse. For example, induction of theophylline

metabolism by phenytoin can occur in a similar manner in the young and the elderly; however, the induction effect of rifampin on drug metabolism is decreased in the elderly.[22] This information is reflected relatively well in the label of drugs recently approved by the United States Food and Drug Administration that are commonly prescribed to elderly patients. In the case of the anticoagulant dabigatran, the effect on CYP enzyme-based metabolic interaction is minimal; however, the drug is a substrate for P-glycoprotein, so attention should be paid for potential P-glycoprotein-mediated inhibition or induction.[23]

There is a possibility that the use of 2 or more agents with similar adverse event profiles causes serious toxicity in the elderly. For example, concomitant use of 2 or more drugs among anti-parkinson agents, tricyclic antidepressants, antipsychotics, anti-arrhythmics, and antihistamines can cause or exacerbate anti-cholinergic symptoms such as dry mouth, blurred vision, constipation, and urinary retention.[24] Indeed, elderly patients should avoid many drugs because adverse events outweigh the benefits of taking the drug. The American Geriatrics Society expert panel periodically updates and publishes the Beers Criteria for potentially inappropriate medication use in older adults.[25]

Considerations for effective pharmacotherapy in the elderly

The amount of a drug required to achieve a desirable effect differs between individuals. Greater variation is observed between elderly patients, and the consensus is that drug doses should be lowered in elderly patients. When prescribing drug therapies it is important to use the minimal dose required to obtain clinical benefit. The “start low and go slow” rule is recommended and involves minimizing the initial dosage, dose titration, and close monitoring according to the condition of the patient.[26] In addition, elderly patients frequently have prescriptions for multiple drugs from more than one doctor; thus, a thorough medical and medication history is important.

Medication non-adherence is a major problem with geriatric

patients. Approximately 50% of elderly patients do not follow directions for taking medication, and often take a lower dose than prescribed.[27] Barriers to compliance include chronic medical conditions, polypharmacy, complex regimens, a higher prevalence of adverse drug reactions, cognitive impairment, and dysphagia.[28] Therefore, it may be necessary to simplify the dosage regimen in order to increase compliance.

Under-representation of the elderly in clinical trials

Older patients are under-represented in clinical trials because they are considered a socially vulnerable population. However, it is not necessarily valid to extrapolate risk-benefit ratios from younger adults to geriatric populations in the absence of evidence. In 1997, a descriptive investigation of 4 major medical journals reported that approximately 35% of clinical studies did not involve elderly patients and did not offer a valid reason.[29] A similar investigation was performed in 2004 and revealed that 15% of clinical studies still excluded the elderly population without legitimate reason.[30] Despite the fact that the elderly represent the majority of patients who die of cancer, they represent one quarter of participants for cancer therapy clinical trials conducted in the United States.[31,32] According to the PREDICT (increasing the PaRticipation of the ELderly in Clinical Trials) study, 64 out of 251 heart failure clinical trials (25.5%) arbitrarily determined the upper age limit of trial participants. Elderly patients were prevented from participating in 109 clinical trials (43.4%) by constraints other than age. For example, patients were excluded because of mild concomitant disease, visual impairment, and hearing impairment, even though there was no cause for concern with the safety of these subjects in the participating clinical trials.[33]

Compared with their younger counterparts, elderly people have increased rates of comorbidities and complications. Besides physical disadvantages, the perceptions of health care professionals and family members can make it difficult for elderly

Table 3. Selected barriers and solutions for participation of the elderly in clinical trials (quoted from Ref.36)

	Patient-Related	Physician-Related	Trial-Related
Barriers	Logistics	Perceptions	Strict inclusion criteria
	Finances	Culture	Poor methods for evaluating functional status
	Lack of understanding of benefits	Complex pharmacokinetics/pharmacodynamics	Lack of funding dedicated to elderly population
	Autonomy	Lack of evidence	
Solutions	Provide transportation	Elder-focused studies	Create geriatric-focused trials
	Provide lodging	Improved communication	Increase/fund studies of elderly population
	Research nurses, trial coordinators	Increase physician training in geriatrics specialty	
	Improved communication		

patients to participate in clinical trials.[34] Such enrollment barriers have gained interest in the past decades.[6] Although numerous solutions have been proposed, implemented solutions have had limited success. It has been suggested that a larger, more succinct effort is necessary from the medical community.[6,35] Barriers and solutions for inclusion of elderly patients in clinical trials are summarized in Table 3.[36] Older participants representative of those seen in clinical practice must be included in clinical trials to better understand the benefits and potential adverse effects of new drugs in the elderly population.[37]

Effort for promoting the inclusion of representative older participants in clinical trials

Many challenges are faced when conducting clinical trials in the elderly. The removal of specific upper age limits from clinical trial protocols, while strongly recommended, was not thought to be sufficient to resolve the under-representation of this patient population [38]. There has been some effort to overcome this through active discussion by experts. A roundtable discussion on the participation of older adults in clinical trials took place at the American Geriatrics Society annual meeting in 2009. It provided an opportunity to discuss the shared views of the American Geriatrics Society, the European Union Geriatric Medicine Society, and regulatory agencies of Europe and United States. The main discussion points are summarized here.[39]

The first challenge is the need to justify inclusion and exclusion criteria clearly. Selection criteria results in the exclusion of older adults with complex illnesses and multiple diseases, who are common in clinical practice. To address this bias, inclusion and exclusion criteria should be clear, simple, and aimed at limiting the number of participants who are considered ineligible because of comorbidity and concomitant medications. The second challenge is the need to reduce dropouts during follow-up. Study design should support the participation of older people who may have difficulty with multiple study visits (e.g., providing transportation or performing home follow-up). The third issue that must be addressed is the difficulty of obtaining informed consent from elderly participants who are often cognitively impaired or have psychiatric problems, such as depression.[40] Careful attention to screening for cognitive impairment, determining that the individual is capable of understanding the risks and benefits of participation, use of objective observers in the consent process, and involving proxy decision-makers when appropriate can help overcome these challenges. The fourth challenge is the need for measurement and adjustment for comorbidity. There are no standards or agreement on how to measure comorbidity in clinical trials. Comorbidity and multiple medications contribute to increased susceptibility to adverse drug events, which can result in selective attrition and missing data. The complexity and heterogeneity of the geriatric population make this standard approach challenging. There are no easy solutions to these concerns, but they highlight the necessity for future research to refine the methodology of clinical

trials performed in older adults with multiple morbidities.[41] Finally, the choice of outcomes relevant to older adults is critical. Some outcomes are likely to be more relevant for assessing efficacy (e.g., cognitive decline and quality of life); others might be more relevant for safety assessment (e.g., falls and delirium). Because older adults are heterogeneous and their response to interventions variable, many outcome measures may not be normally distributed. This possibility must be taken into account in the design and analysis of clinical studies.

Despite challenges, it is imperative that geriatric society organizations and patient advocacy groups work together to halt age discrimination in clinical trials. Older people who are more characteristic of those seen in clinical practice must be included in clinical trials to achieve the goal of safe and effective drug therapy for this growing patient population.[39]

Conclusion

Ultimately, the goal of medical intervention in older patients is to improve the quality of the remainder of their life. Drug therapy is the most important intervention directed toward this goal. Clinical pharmacology, drug efficacy, and drug safety differ in elderly patients compared with their younger counterparts. Therefore, a different approach is necessary to provide optimal care to these complex patients. The geriatric dosing axiom, “start low and go slow” is based on pharmacokinetic considerations and concern for adverse drug reactions, rather than clinical trial data. Sound evidence through prospective clinical trials is essential especially in elderly patients with multiple comorbidities and polypharmacy who are more typical of the patients seen in clinical practice. The design of clinical trials should consider the inclusion of these complex older patients and make provisions for concerns about the higher complexity of the trials, such as multiple measurements, higher attrition rate, multicenter heterogeneity, and higher costs. Therefore, geriatric societies, governments, and patient advocacy groups should collaborate to generate widespread support to promote the inclusion of older people in clinical trials. It is believed that all involved in clinical trials have both an obligation and an opportunity to eliminate age discrimination in clinical trial practice.

Conflict of Interest

The author has no conflicts of interest.

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