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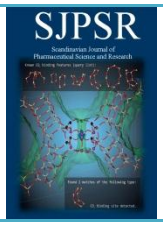

PHARMACOKINETICS IN GERIATRIC PATIENTS

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ABSTRACT

The complex process of aging is characterized by progressive loss in the functional capacities of organs, a reduction in mechanisms of homeostasis, and altered response to receptor stimulation. Medication therapy is among the most widely used and highly valued interventions for acute and chronic diseases of older adults, yet the use of drug therapy in the geriatric patient is one of the most difficult aspects of patient care. Alteration of the pharmacokinetics of these drugs in the elderly may necessitate adjustment of drug dosages to prevent toxicity or inadequate therapy. Recognition of the relationship between physiologic changes and drug pharmacokinetics is important to better prescribe the correct dose in the elderly population.

INTRODUCTION

Usually, elderly is defined by a chronological age of 65 years or older. One should be aware of the great variability in pharmacokinetics and pharmacodynamics in the elderly. Physiologic changes that occur in the aging process may directly affect drug pharmacokinetics. The complex process of aging is characterized by progressive loss in the functional capacities of organs, a reduction in mechanisms of homeostasis, and altered response to receptor stimulation. These changes combine to increase the susceptibility of elderly individuals to environmental and physical stressors as well as the effects of medications. The prevalence of diseases increases with advancing age and this increase is accompanied by an increase in the use of medications. Medication therapy is among the most widely used and highly valued interventions for acute and chronic diseases of older adults, yet the use of drug therapy in the geriatric patient is one of the most difficult aspects of patient care. Alteration of the pharmacokinetics of these drugs in the elderly may necessitate adjustment of drug dosages to prevent toxicity or inadequate therapy [1,2,3].

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PHYSIOLOGICAL CHANGES

Cardiac structure and function

Aging is typified by changes in the cardiovascular system including a decrease in cardiac output and increase in vascular resistance. The heart becomes more dependent on blood volume (preload). Decreases in cardiac output lead to decreased hepatic blood flow. Because most analgesics are metabolized by the liver, decreased blood flow may result in decreased metabolism and prolonged excretion of medications [1, 2, 4, 5].

Renal system

Renal function declines progressively with age. This varies between individuals, with some experiencing very little decline in glomerular filtration rate. On average, glomerular filtration rate decreases less than 1 ml/min/year after middle age. Although primary renal aging occurs, diabetes, hypertension and vascular disease play a significant role in worsening renal function. Despite the decline in glomerular filtration rate, there is no concomitant increase in plasma creatinine because of age – related loss of muscle mass. Therefore, creatinine is not a reliable indicator of glomerular filtration rate in the elderly subject. Acid-base balance is maintained under physiological conditions but a reduced response to stress is revealed by the inability to deal with acid loads, which may be due to defective renal tubular secretion of ammonium ions. Decreased renal function can lead to toxic

accumulation of drugs and metabolites if dosing is not adjusted according to renal clearance [6-10].

Gastrointestinal system

Stomach and duodenum

The main changes involve the secretion of hydrochloric acid and pepsin, which are decreased under basal conditions.This maybe the direct consequence of changes in the enzyme secreting cells and organs or hormonal and neural regulatory alterations. By contrast, gastric emptying in elderly subjects is similar to that of young subject [1, 2, 11].

Small Intestine

Advancing age is accompanied by reduced absorption of several substances (e.g. sugar, calcium, iron) while digestion and motility remain relatively unchanged.

Colon

The studies investigating the relationship between age and colonic motility have shown conflicting results. In one study, elderly subjects had a slower colonic transit time of radio labeled plastic particles than young subjects. No significant age- related changes in colonic transit time have been observed in a recent study comparing young and middle-aged subjects.

Liver

Advancing age is associated with a progressive reduction in liver volume and liver blood flow. Alteration of hepatic structure and enzymatic functions with ageing is moderate. In the healthy elderly person, routine tests of liver function involving the metabolism and elimination of specific dyes, radio isotopes, and protein synthesis do not show significant differences between individuals aged 50–69 and 70–89years.

Body composition

Significant changes in body composition occur with advancing age. There is a progressive reduction in total body water and lean body mass, resulting in a relative increase in body fat [1, 2, 7].

PHARMCOKINETIC PARAMETERS OF DRUG ABSORPTION DISTRIBUTION AND ELIMINATION

Drug Absorption

Most drug absorption is via the gastrointestinal tract after oral ingestion. Elderly persons may have decreased gastrointestinal motility and gastrointestinal blood flow and increased gastric PH. These age related changes wood be expected to decrease gastrointestinal drug absorption; however, decreased intestinal motility results in a longer time for absorption is quantitatively unaffected by aging.

Little information exists on the absorption of delayed release formulation in elderly patient or on the absorption of transdermal, transbuccal or transbronchial drug administrations in this group [1,2,5].

Drug distribution

The volume of distribution (Vd) is not an actual physiological measurement but is an important pharmacokinetic measurement. Volume of distribution is defined as the amount of drug in the body divided by the concentration of drug in the blood or plasma per kilo gram of body weight. A value for Vd greater than the volume of blood or plasma would suggest that a drug has partitioned into or has become bound to tissue components.

Loading Dose(mg/kg)=Desired Blood concentration(mg/L) X volume of Distribution (L/kg)

The potency and duration of action of certain drugs are increased as both liver size and hepatic blood flowed crease along with subsequent the patic in activation Renal function is decreased similarly, resulting in higher plasma levels of free drug. The characteristic changes observed in elderly persons are further exacerbated in patients with congestive heart failure.

Many drugs used in therapy bind to plasma proteins in varying degrees. Free drug concentrations determine pharmacological effect because bound drug cannot bind to tar- get tissues but instead can serve as a drug reservoir. Basic drugs are bound by α1-acidglycoprotein, but this binding is not altered with aging. Most drugs are acidic and are bound by serum albumin; total serum albumin and therefore drug-binding capacity decrease approximately 12% in elderly people. A substantial increase in the fraction of free drug can occur if a drug is displaced from plasma albumin by a second drug. The conditions necessary for a notable drug-drug interaction are (1) the drug is highly bound to value of Vd greater Diseases common in elderly people can depress albumin. These include some chronic debilitating diseases that require drug therapy, such as heart failure, renal disease, rheumatoid arthritis, hepatic cirrhosis, and some malignancies. Elderly persons require reduced doses of narcotics to achieve analgesia without unwanted depressant effects; the probable cause of this is discussed in the section, "Renal Excretion of Drugs in the Elderly Population." Decreased protein binding is believed to contribute to the need to adjust doses for elderly patients. Studies on intravenous meperidine plasma concentration in control and surgical patient groups found that older patients had higher unbound (free) drug fractions. Similarly, the binding capacity of warfarin was found to decrease proportionally to the lower plasma albumin levels found in the elderly population. Other highly protein-bound drugs include phenytoin, diazepam, chloramphenicol, indomethacin, and furosemide [1,2,47].

Drug Elimination

The duration and magnitude of both therapeutic and adverse effects of drugs relate to the level of drug in the blood; thus, the process that eliminate drugs from the blood become important considerations .Knowing that a specific amount of a drug has undergone bio transformation or has been removed physically by filtration into the urine is not enough information to understand the importance of this action. This is belter expressed by 2 pharmacological concepts, clearance and half life, which are important to understanding adverse drug reactions in the elderly population [1,2,6,7,8].

Drug Clearance

Clearance is the measure of fractional loss of drug per unit time. The unit of clearance, milliliters per minute per kilogram, is derived from the ratio of drug elimination by all routes (amount/time) and the concentration of the drug(amount/volume),normalized by being expressed per kilogram of lean body weight. Stated in another way, clearance is the amount of blood flow completely extracted of drug per unit time. It represents the efficiency of drug extraction from blood. Clearance does not indicate how much drug is being removed, but rather the volume of plasma that would need to be completely freed of drug to account for the elimination of the drug.

For example, an individual with a renal plasma flow of 700 mL/min and a drug extraction of 25% has a renal clearance of 175 mL/min. Clearance values typically are expressed as per kilogram of body weight to facilitate comparison between individuals. The greater the clearance, the more rapidly a drug is removed from blood or plasma [5-7].

Half-life

After drug distribution has occurred, the half-life of a drug is the time it takes for the drug concentration in plasma to decrease by 50%.The clinically relevant half-life of a drug is the function of both its $_{Vd}$ and clearance; thus, a change in either of this parameters will alter half-life.

t ½=0.693XVD/Clearance

Although time spent in the absorption phase is a factor, a clinical rule of thumb for attaining better than 90% of C is that approximately 4 doses are needed, administered once every half-life of the drug; 4 half-lives are needed to re- move 90% of the drug from the body. Therefore, the half- life provides information necessary to determine dosing intervals or the time necessary for stabilization or reduction in effects of the drug related to drug concentrations.

The elimination half-life of drugs increases with age. This may be due to decreases in drug clearance or increases in distribution. The half-lives of the following drugs have been found to increase in elderly persons: digoxin, chlorpropamide, quinidine, diazepam, propranolol, erythromycin, nifedipine, ampicillin, prazosin, aspirin, lisinopril, ranitidine, enalapril, and lithium. In summary, the half-life of a drug determines the dosing interval; the volume of distribution determines the loading dose of a drug; and the clearance of a drug determines the dose of drug that must be administered per unit time [6,7].

Hepatic Drug Metabolism

For some drugs, hepatic metabolism is highly dependent on blood flow. Liver blood flow can decrease significantly with increasing age and is further compromised in the presence of congestive heart failure (CHF). With drugs that are highly dependent on hepatic metabolism (e.g., most beta-blockers, lidocaine, and narcotic analgesics), a decrease in hepatic clearance can increase the drug concentration and lead to toxicity. In addition to altering hepatic blood flow, age influences the rate of hepatic clearance by causing changes in the intrinsic activity of selected liver enzymes. This age-related process has been found in the Phase I enzymatic pathway. Common drugs using this pathway and having the potential for metabolism influenced by age includes the longer acting benzodiazepines such as diazepam, chlordiazepoxide, and clorazepate.

Drugs that undergo hepatic Phase II enzymatic biotransformation (e.g., *lorazepam*, *oxazepam*, and *temazepam*) do not appear to be adversely affected by age; therefore, they are preferred agents for older patients. At all ages, drug metabolism can be affected by genetics, smoking, diet, gender, comorbid conditions, and concomitant drugs. The cytochrome P (CYP) 450 enzyme system, primarily a part of the Phase I hepatic metabolism pathway, can be affected by many drugs. Of the more than 30 CYP 450 isoenzymes identified to date, the major ones responsible for drug metabolism include CYP3A4, CYP2D6, CYP1A2, and the CYP2C subfamily. Newer evidence in geriatric patients has shown a reduction in CYP2C19 activity, no reduction in CYP2D6 activity, and marked variability with little change in the CYP1A2, CYP2C9, CYP2E1, and CYP3A4isoenzymes.

Hepatic Disease

Any impairment of normal liver function potentially will alter hepatic biotransformation. A disproportionate number of elderly patients have liver disease associated with excess alcohol use, gallstones, cholangitis, gallstone-induced pancreatitis, biliary cirrhosis, and fatty livers associated with diabetes or obesity. Adverse drug reactions may suggest liver dysfunction. The degree to which CYP mono oxygenase activity and hepatic elimination are decreased is a function of the severity of liver damage. A decreased hepatic biotransformation of tolbutamide, diazepam, and morphine in patients with hepatic dysfunction has been associated with exaggerated pharmacological responses. Decreases in hepatic blood flow resulting from cardiac in sufficiency or β-adrenergic blockade also can affect the rate of hepatic

biotransformation. The metabolism of drugs with a high hepatic extraction ratio is limited by liver blood flow. For such drugs, a decreased hepatic blood flow results in decreased rates of biotransformation and clearance of the parent drug and therefore a prolonged effect. Examples of drugs with high extraction ratios whose elimination likely is altered by changes in liver blood flow are lidocaine, propranolol, verapamil, and amitriptyline [1,2,6-8].

Renal Excretion of Drugs in the Elderly Population

Renal blood flow is reduced by approximately 1% peryearafterage50years.Many drugs, active and inactive, are excreted by the kidneys. A reduction of renal function can affect the elimination of a drug if it is more than 60% excreted by the kidneys. Higher blood levels of drugs whose elimination is primarily renal are found when the glomerular filtration rate decreases. This may result in accumulation of drugs producing higher drug levels for prolonged periods of time. Some drugs excreted primarily by the kidneys include atenolol, sotalol, digoxin, lithium, amphotericin, pentamidine, procainamide, cimetidine, allopurinol, chlorpropamide, and many antibiotics.

The assessment of renal function in elderly persons may not be quantified accurately by the serum creatinine level alone. Because creatinine formation is a function of muscle mass, a normal serum creatinine level may be seen when the reduction in creatinine clearance or glomerular filtration is substantial. Differences in creatinine clearance correlate with an approximate 2-fold increase in the half-life of penicillin in the elderly patient. Similarly, decreases in digoxin clearance occur in the elderly patient compared with the younger patient [1, 2, 3, 6-9].

Table 1. Relation shop of Age to Drug Cleared by Hepatic Biotransformation

Drug or metabolite	Initial pathway of bio transformations
Age-related reduction in clearance	
Antipyrine	Oxidation (OH, DA)
Diazepam	Oxidation (DA)
Chlordiazepoxide	Oxidation (DA)
Desmethyl diazepam	Oxidation (OH)
Clobazam	Oxidation (OH)
Small or negligible age-related change in clearance	
Oxazepam	Glucuronidation
Lorazepam	Glucuronidation
Temazepam	Glucuronidation

Table 2.Physiologic Changes with Aging that May Affect Pharmacokinetics

Process	Physiologic Effect
Absorption	Reduced gastric acid production Reduced gastric emptying rate Reduced GI motility Reduced blood flow Reduced absorptive surface
Distribution	Decreased total body mass Increased percentage of body fat Altered relative tissue perfusion Altered Protein binding
Metabolism	Reduced live mass Reduced live blood flow Reduced hepatic metabolic capacity Reduced enzyme activity Reduced enzyme induction
Excretion	Reduced renal blood flow Reduced glomerular filtration Reduced renal tubular secretory function
Tissue sensitivity	Alterations in receptor number Alterations in receptor affinity

	Alterations in second messenger function[a] Alterations in cellular response Alterations in cellular nuclear response

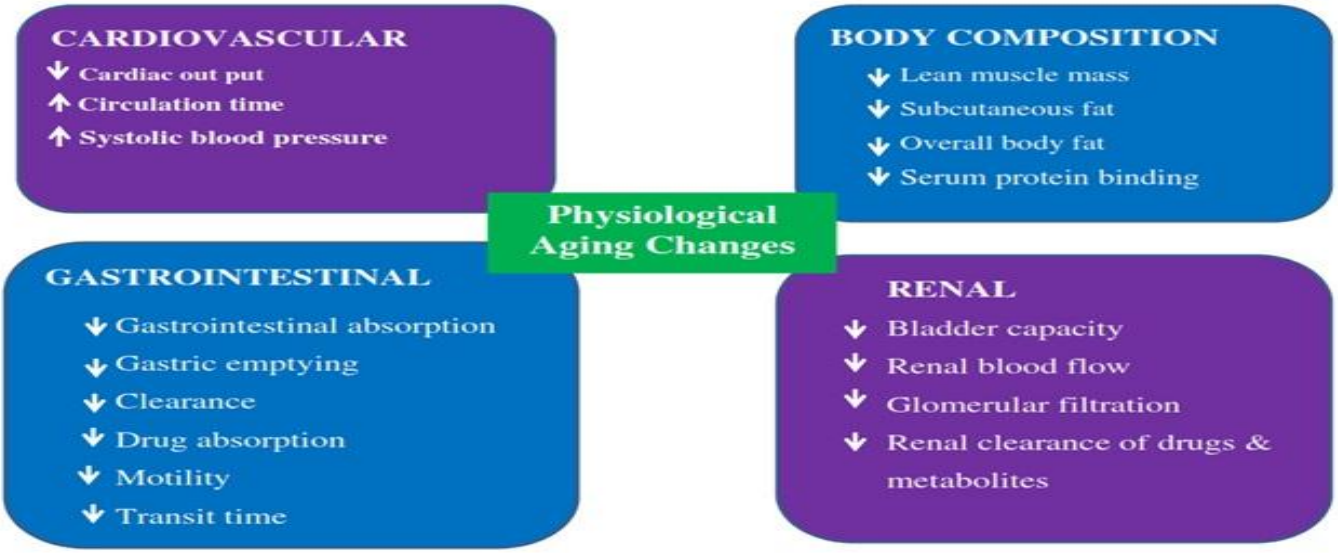
Table 3. Drugs with Increased Bioavailability in the Elderly

Amitriptyline	Lidocaine
Chlordiazepoxide	Metroprolol
Desipramine	Propranolol

Table 4.Effects of Age on Plasma Protein Binding of Select Drugs in Geriatrics

Drugs with decreased protein binding (increased free fraction)
Acetazolamide Lorazepama Carbenoxolone
Drugs with increased protein binding (decrease free fraction)
Denazeprilat Haloperidol Ceftriaxone
Select Drugs with no change in protein binding
Alprazolam Metoprolol Caffeine

Fig no 1. Physiological Changes during Aging



CONCLUSION

Advanced age is associated with significant changes in physiological functions which affect pharmacokinetics of many drugs used to treat or prevent diseases. Renal and hepatic elimination of many drugs are reduced in the elderly, leading to a prolonged elimination half-life and increased risk of adverse effects. Knowledge of the consequences of aging and of why pharmacokinetics may be modified in the elderly population should be known to avoid adverse drug reaction.

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