Pharmacokinetic considerations in geriatric medication

ABSTRACT

In this century, the ageing of a population has become a major demographic issue all around the world. Ageing is much more than a process of functional degeneration; it also generates anatomical and physiological variations which, if they proceed beyond a certain point, might result to decompensation of the relevant system. Although the elderly have a greater rate of many GI problems (e.g., dyspepsia, diarrhoea, and constipation), ageing seems to have only a minor significant influence on most GI activities, due to the GI tract's functional reserve capacity. Ageing is associated with some reduction in first-pass metabolism that might be due to a decrease in liver mass and perfusion. It has recently been proposed that decreases in the mass of individual organs/tissues can contribute to a decrease in resting metabolic rate, which in turn promotes changes in body composition favouring increased fat mass and decreased fat-free mass with age. Basic drugs (lignocaine, propranolol) bind primarily to a1-acid glycoprotein, while acidic drugs (diazepam, phenytoin, warfarin, salicylic acid) bind to albumin. Regardless of the fact that there are no notable age-related variations in the concentrations of both of these proteins albumin is generally reduced in malnutrition or acute illness, while a1-acid glycoprotein is commonly raised during acute illness. Although nearly every tissue/organ, like the intestinal wall, lung, skin, and kidney, can metabolise medicines to some degree, the liver is a major organ of drug metabolism. Reduction in renal function in elderly subjects, particularly glomerular filtration rate, affects the clearance of many drugs such as water-soluble antibiotics, diuretics, digoxin, water-soluble badrenoceptor blockers, lithium and nonsteroidal anti-inflammatory drugs.

1. INTRODUCTION

In this century, the ageing of a population has become a major demographic issue all around the world. The physiological and functional capacities of the body change considerably as we age. This can have an impact on the pharmacokinetic (PK) and pharmacodynamic (PD) characteristics of drugs in the elderly, resulting in clinically relevant safety and efficacy consequences. Increased prevalence of sickness, as well as age-independent factors like lifestyle, can all affect drug pharmacology. Polypharmacy also raises

the risk of PK and PD drug-drug interactions being altered. This renders treatment for the elderly more difficult [1].

Patients between the ages of 18 and 64 are typically included in clinical trials undertaken in the adult population. Drugs, on the other hand, should be investigated in individuals of all ages, and test subjects should be representative of the population of patients who would get the therapy in daily medical practise. Clinical trials have a low representation of elderly patients. Regulatory authorities in industrialised nations have urged researchers and industry to stop setting unjustified upper age limitations and to not exclude old persons from clinical trials only if there is a worthy cause. Since a few years, the Indian regulatory authority has imposed a maximum age limit for research undertaken in the country [2].

Aging is a collective term used to refer to the combination of cumulative local impacts at the molecular, cellular, and tissue levels. Although it is hard to define ageing, certain traits are established. The most reliable is the loss of functional units over time. These are the tiniest structures still involved in executing the particular physiological functions of the organ to which they belong (e.g., nephrons, alveoli, or neurones). Distortion of several regulatory systems that promote coordination and integration between cells and organs is also another feature. This drop in functional reserve is linked to a reduction in survivability and an increase in susceptibility. Ageing is much more than a process of functional degeneration; it also generates anatomical and physiological variations which, if they proceed beyond a certain point, might result to decompensation of the relevant system. The physiological changes that occur as people get older are described [3].

2. Physiological And Pharmacokinetic Changes associated with age

2.1. Absorption

There appears to be a rise in gastrointestinal (GI) problems with age, and certain slight variations in the GI tract have been noted [4,5]. Although the elderly have a greater rate of many GI problems (e.g., dyspepsia, diarrhoea, and constipation), ageing seems to have only a minor significant influence on most GI activities, due to the GI tract's functional reserve capacity [6]. The question of whether stomach emptying varies with age is still debated [7]. Madsen and Graff found that older age had no influence on gastric emptying [8], while Shimamoto et al. observed that postprandial peristalsis and stomach contractile force were diminished in the elderly [9].

Many retrospective studies made between 1920 and 1980 suggested that gastric acid secretion declines with increasing age. The number of patients who were chronically hyposecretors had serum indicators of atrophic gastritis [10]. Advancement of age had no impact on stomach acid secretion in Helicobacter pylori-negative subjects, but it had in Helicobacter pylori-positive patients because of the high likelihood of fundic atrophic gastritis with age [11, 12]. Moreover, ageing is linked to lower in splanchnic blood flow and a decrease in intestinal surface area [13]. Absorption of several substrates, including the majority of oral antiarrhythmic medications, are generally unaffected in the elderly if it is accomplished by passive diffusion [14]. However, increasing data suggests that drug uptake and extrusion in GI epithelial cells are

mediated by transporters, and that active transfer processes are the standard rather than the exception [15-17]. Vitamin B12, iron, calcium, magnesium, and leucine absorption, which is done via active transport pathways, appears to be hampered in the aged [18]. Nevertheless, insufficient studies have been done on the impact of ageing on the expression and activity of these GI transporters.

2.2. Presystemic metabolism and biotransformation

When considering oral bioavailability, presystemic elimination by the intestinal mucosa and during first pass through the liver has to be taken into account). Ageing is associated with some reduction in first-pass metabolism that might be due to a decrease in liver mass and perfusion [19]. Some medications with considerable first-pass metabolism, such as propranolol and labetalol, can have markedly enhanced bioavailability and, as a consequence bioavailability [20, 21]. Other high clearance (CL) medications, like verapamil [22] or propafenone [23] have identical bioavailability in both young and old individuals. But at the other hand, the first-pass activation of some prodrugs, like the ACE inhibitors enalapril and perindopril, may be slowed or decreased, leading to a reduction in bioavailability [24]. Drugs like buprenorphine, which may have a low bioavailability when taken orally, benefitted from transdermal administration.In the elderly transdermal drug administration is an ideal therapeutic approach for chronic pain and some neurological disorders because it provides sustained effective plasma levels, it is simple to use, and it may reduce systemic adverse effects [25]. Transdermal fentanyl absorption is thought to be lowered in the elderly, possibly requiring dose adjustments, but while transdermal buprenorphine absorption is unaffected by age [26]. Even so, most transdermal devices in the older people even now require long-term evaluation to understand better how age-related skin changes will affect drug absorption.

2.3. Distribution

It has recently been proposed that decreases in the mass of individual organs/tissues can contribute to a decrease in resting metabolic rate, which in turn promotes changes in body composition favouring increased fat mass and decreased fat-free mass with age. [27, 28, 29]. When body fat increases and total body water and also lean body mass reduce, polar drugs that are predominantly water-soluble, such as digoxin, ethanol, theophylline, and aminoglycosides, have a relatively small apparent volume of distribution (V), and hence plasma concentrations rise [30]. Nonpolar compounds, on the other hand, are lipid-soluble (e.g., diazepam), so in the elderly V increases and the half-life (t1/2) is prolonged [31]. There is a correlation ($P = 0.053$) between drug lipophilicity and the effect of ageing on V. The loading dose necessary to begin therapy is calculated by the term V, and loading doses are computed depending on the desired steady-state blood level and V: Loading dose (mg/kg) = target blood concentration (mg/L)/ Distribution volume (L/kg.) As a consequence, hydrophilic drugs such as digoxin and aminoglycosides will have a lower initial dose requirement [32]. Nevertheless, for the majority of drugs, these age-related

changes in body composition will have little effect on V, and adjusting loading doses is unlikely to be essential.

This apart from changes in body composition, there are slight variations in plasma protein binding with age. Serum albumin concentrations in the older people can be reduced slightly or remain constant; 1-acid glycoprotein levels tend to increase with age [33]. These changes are generally not attributed to age per se, but rather to pathophysiological changes or disease states that are more prevalent in the older people Only very strongly bound medicines with a small V and a narrow therapeutic index might be clinically important if alterations in plasma protein binding occur. In such cases, only a slight increase in free drug concentration can have pharmacodynamic effects. Although plasma protein binding may play a major role in medication interactions, it is believed to be of small therapeutic importance because the initial and temporary effect of protein binding on free plasma concentration is quickly offset by enhanced elimination [34].

2.4. Metabolism

Although nearly every tissue/organ, like the intestinal wall, lung, skin, and kidney, can metabolise medicines to some degree, the liver is a major organ of drug metabolism. Many cytochrome P450 (CYP)-dependent phase I processes (e.g. oxidation, reduction) and/or phase II pathways are needed for the biotransformation of the great majority of drugs (e.g. glucuron idation, acetylation, and sulfatation). Some drugs are metabolised in phase I and then phase II reactions, while many are metabolised in only one of these modes [35]. The interdependence of drug metabolism and transport on drug disposition has now received a lot of attention, and it has been named "transportmetabolism interaction" [36, 37]. They can influence the pharmacokinetics of a drug and also drug interactions for inhibitors of CYP3A and P-glycoprotein by acting independently, in conjunction with each other, or via compensatory mechanisms (P-gp). The ultimate outcomes of drug elimination from the body are hard to forecast since they are dependent on the inhibitory capability of a drug for both systems. These transport pathways, and even the oxygen supply to the hepatocytes (which is essential for phase I reactions), may exhibit some age-related variations (caused by age-related changes of membrane structures). Nevertheless, any evidence is currently unavailable. During the ageing process, the liver has a tremendous regenerative capacity and retain its functioning. On a cellular and physiological level, however, there are slight variations that can affect the liver's overall function. Increased age is correlated to a fall in hepatic volume of 20 to 30% [38] as well as a reduction in hepatic blood flow of 20 to 50%.[39]. These modifications may have an influence on the elimination of high-clearance medicines in general. The volume of hepatocytes in the older, on the other side, stays unchanged. Additionally, there are still no specific age-related liver ailments and routine clinical tests of liver function do not vary substantially with age, the course and outcome of some liver diseases can be affected by age [40,41]. The characteristic of high or low extraction of a drug by the liver has been attributed to whether the metabolic CL of a drug falls or remains unchanged with age. Some drugs with a high extraction ratio and a high intrinsic CL (“blood flow-limited metabolism”) are rapidly

metabolised in the hepatocytes, with hepatic blood flow restricting the rate of drug loss. They may indicate a reduction in metabolic CL as they get older. The metabolic CL of drugs with low hepatic extraction, on the other hand, is seldom diminished since it is dependent largely on the enzyme activity in the liver ("capacity-limited metabolism") , instead of on hepatic blood flow. Changes in hepatic blood flow and innate CL, on the other hand, do not explain why certain drugs (like antipyrine and theophylline) exhibit a minor (about 20%) age-dependent decline in hepatic metabolism [42].

2.5. Protein binding

Basic drugs (lignocaine, propranolol) bind primarily to a1-acid glycoprotein, while acidic drugs (diazepam, phenytoin, warfarin, salicylic acid) bind to albumin. Regardless of the fact that there are no notable age-related variations in the concentrations of both of these proteins [43,44], albumin is generally reduced in malnutrition or acute illness, while a1-acid glycoprotein is commonly raised during acute illness. The significance of such variations, although, needs to be determined, given the key factor affecting drug effect is the drug's free concentration. Although plasma protein binding could theoretically play a role in pharmacological interactions or physiological effects for highly protein bound medicines, its clinical utility is minimal. This is attributed to the reason that protein binding's initial and temporary effect on free plasma concentration is soon counterbalanced by its effects on clearance [45].

2.6. Kidney clearance of drugs

Reduction in renal function in elderly subjects, particularly glomerular filtration rate, affects the clearance of many drugs such as water-soluble antibiotics [46,47], diuretics [48], digoxin [49], water-soluble badrenoceptor blockers [50], lithium [51], and nonsteroidal anti-inflammatory drugs [52,53]. The therapeutic significance of these declines in renal excretion is governed by the drug's expected toxicity. Aminoglycoside antibiotics, digoxin, and lithium, which all have a narrow therapeutic index, are likely to trigger considerable side effects if they accumulate even little more than anticipated. A recent research, although, raised questions on the importance of age-related loss of kidney function in pharmacokinetics. Although creatinine clearance is rather less in healthy elderly people, atenolol, hydrochlorothiazide, and triamterene excretion was equivalent to those of young adults [54].

2.7. Liver clearance of drugs

The capability of the liver to remove the drug from the blood traveling through the organ and the amount of hepatic blood flow govern drug clearance, as shown by the formula below:

$$Cl_{liver} = Q\frac{[Ca-Cv]}{[Ca]} = QE$$

where E = steady-state extraction ratio

Q = liver blood flow (sum of hepatic portal and hepatic arterial blood flow

[Ca] = concentration of drug in portal vein and hepatic artery

[Cv] = concentration of drug leaving the liver in the hepatic vein, and

CL_{liver} = clearance by the liver.

As a consequence, the liver's clearance is affected by both blood flow and extraction ratio. The latter is based on the liver's ability to metabolise. Drugs are categorized depending on their extraction ratio:

i. Chlormethiazole, dextropropoxyphene, glyceryl nitrate, lignocaine, pethidine, and propranolol are examples of drugs with a high extraction ratio (E > 0.7).

ii. Aspirin, codeine, morphine, and triazolam are examples of intermediate extraction ratios (E 0.3–0.7).

iii. Carbamazepine, diazepam, phenytoin, theophylline, and warfarin have a low extraction ratio (E 0.3).

CL is rate-limited by perfusion when E is high. Cv is similar to Ca when E is low, and fluctuations in blood flow produce slight alterations in CL. As a consequence, the decline in liver blood flow that occurs with ageing has a significant impact on the clearance of drugs with a high extraction ratio. Many medications metabolised by phase-1 routes in the liver have exhibited substantial reduction in clearance in many studies [55,56]. Since this activity of drug metabolising enzymes is retained, the key factor is quite likely age-related variations in liver size and hepatic blood flow [57]. Monooxygenase activities are sustained in even advanced old age, as per research on human liver tissue [58]. *In vivo* investigations employing radiolabelled erythromycin breath tests as CYP3A activity probes [59] supported these conclusions. It's uncertain whether enzyme response in humans varies when they get aged. According to several pharmacokinetic studies, factors such as cigarette smoking do not induce drug metabolism that much in older people as they do in young adults [60]. Analogous theophylline clearances were demonstrated experimentally in both old and young people who smoke [61]. Also there are contradictory findings on the provoking effects of different drugs [62,63]. The evidence for enzyme inhibition in old age is much more consistent, for most human research reporting enzyme inhibition comparable to those seen in young adults [64,65]. The influence of aging process on conjugative metabolism have rarely been examined. In general, studies found no significant impacts of ageing on conjugation routes [66–70]. It has recently been shown that a decrease in renal function can have a substantial impact on medicines that are not only eliminated by the kidneys but also undergo considerable metabolism in the liver Kidney damage has been related to a drop in liver cytochrome P450 activity as a result of lower gene expression .As a consequence, the age-related loss in kidney function may have an impact on drug metabolism in the liver [71–73]. To fully understand this point, further study is necessary.

Table 1 Summary of changes is pharmacokinetic parameters with age [74]

Parameter	Change	Effect
Absorption	Increased pH in the stomach Gastric emptying is delayed splanchnic blood circulation is	Absorption is somewhat reduced (Occasionally clinically significant)

	Reduced Reduced absorption surface	
Distribution	Rise in body fat	Enhanced volume of distribution and half life of lipophilic drugs
	Lean body mass is reduced	
	Total body water is reduced	Plasma concentration of water soluble drugs is enhanced
	Serum albumin is reduced	Free proportion of highly protein-bound acidic drugs in plasma is enhanced
	Alpha 1-acid glycoprotein is enhanced	Free fraction of basic drugs is lessened
Metabolism	Reduction in hepatic blood flow	First-pass metabolism can be less effective
	Reduction in hepatic mass	Some medicines' phase I metabolism may be slightly hampered; phase II metabolism is recovered.
Excretion	Reduction in renal blood flow and glomerular filtration rate	Drug clearance by the kidneys might be hampered to varying degrees

Table 2 Geriatric pharmacokinetics of some specific drugs

Name of drug	Absorption	Distribution	Drug clearance through kidney	First-pass metabolism and bioavailability	Reference

Cyanocobalamin, iron and calcium	Reduced				75, 76
Levodopa	Enhanced				77
Gentamicin, digoxin, ethanol, theophylline, and cimetidine		Enhanced			78, 79,80
diazepam, thiopentone, lignocaine, and chlormethiazole		Enhanced			81, 82 83, 84,85
Hydrophilic antibiotics, diuretics, digoxin, hydrophili beta - adrenoceptor blockers, lithium and nonsteroidal anti-inflammatory			Reduced		86,87,88 89,90,91, 92, 93
atenolol, hydrochlorothiazide and triamterene			No change		94
chlormethiazole, dextropropoxyphene, glyceryl nitrate, lignocaine, pethidine, and propranolol					95,96

ropranolol and labetalol				First pass metabolism decreased Increased	97, 98, 99
ACE inhibitors such as enalapril and perindopril are prodrugs				First pass metabolism is slowed decreased bioavailability	100

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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