Drug Therapy in the Elderly

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This review examines altered drug responses during aging. The incidence of diseases and disorders that require drug treatment rapidly increases with advancing age; elderly patients tend to receive more medications more often and are therefore at a correspondingly higher risk of experiencing adverse drug reactions and interactions. The cognitive decline that commonly accompanies aging can exacerbate this problem, with elderly individuals becoming confused and forgetful about their prescribed medications. Physiological responses to drugs depend on several factors, including the time course of drug absorption, distribution, metabolism, and elimination in the body (pharmacokinetics), and the actions of these drugs at the intracellular level (pharmacodynamics). As people age, the pathophysiologic processes of aging will influence all of these factors, including the time course of drug concentration in the body and target organ sensitivity. These age-related pharmacokinetic and pharmacodynamic effects must always be kept in mind by those responsible for the medical care of the elderly.

IT HAS BEEN estimated that in the present decade in the United States, there will be a large increase in the number of individuals 85 years of age and older, compared to previous decades such as 1960 to 1970.[1] This demographic change will inevitably give rise to an increasing demand for medications, as well as for new knowledge about the effect of the aging process on drug actions and interactions. It is well known that the pathophysiologic changes that occur in the transition from middle age to old age alter responsiveness to drugs. In the United States, as many as 28% of hospital admissions of elderly patients are the direct result of drug-related problems, with 70% being attributable to adverse drug reactions (ADRs).[2] ADRs add an unnecessary cost to an already burdened health care system and are usually preventable. The physiologic response to drugs is dependent on several factors, including the time course of drug absorption, distribution, metabolism, and elimination in the body (pharmacokinetics) and the effect of drugs on the target cells (pharmacodynamics).[3]

PHARMACOKINETIC CHANGES IN AGING

Rates of Dissolution and Absorption

In order for an orally administered drug to reach the bloodstream and then the target organ, it first needs to dissolve and then be absorbed. If the dissolution process is slow because of reduced saliva, gastric, and intestinal fluids, the rate of absorption decreases (increased T_{max}) without affecting the total amount of drug absorbed.[3] Drugs that need to be absorbed rapidly by the buccal mucosa, such as glyceryl trinitrate, will be absorbed at a slower rate in the elderly since the amount of saliva produced decreases with age. The same is true of gastric fluid, which is reduced with advancing age,[4] along with reduced acidity, weaker peristalsis, and delayed gastric emptying. These changes delay absorption of drugs in the stomach. In the intestine, there is a reduction in the jejunal surface area[5] and therefore the absorption of drugs that depend on passive diffusion to enter the bloodstream is slower, with a correspondingly longer time required to achieve peak drug effects. Table 1 summarizes this information. In addition there is a reduction in splanchnic blood flow,[6] which further prolongs the time needed for drug absorption.[7]

Most drug absorption from the gastrointestinal tract is by passive diffusion and there is little evidence to suggest that there are significant age-related changes in the amount of drug absorption,[8] with one exception—levodopa.[3] The amount of levodopa absorbed is increased in the elderly because dopa-decarboxylase levels in the gastric mucosa diminsh with age and, therefore, less levodopa is degraded in the stomach . Some drugs (such as vitamin B_{12}, iron, and calcium) that enter the bloodstream by active transport mechanisms are poorly absorbed in the elderly. Reduced gastric acidity in aging has not been shown to affect drug absorption.[9] However, important changes are seen in the elderly when it comes to drug-drug interactions.[8] For example, antacids decrease the oral absorption of H2-antagonists (eg, cimetidine), and alcohol accelerates the absorption of chloral hydrate.[8]

Distribution

The distribution of drugs in the body in the elderly is related to either changes in body fat and water or to changes in protein binding. With aging, cardiac output is reduced and peripheral vascular resistance increases so that the total systemic perfusion of organs including the liver and kidneys goes down. This reduction in organ perfusion, in turn, decreases the body's ability to metabolize and excrete drugs. In the older person, lean body mass can decrease by as much as 12% to 19%,[9] resulting in an increase in the blood levels of drugs that are primarily distributed in muscle (eg, digoxin). Adipose tissue mass may increase 14% to 35% in the elderly, even in the absence of overt obesity. Total body water content decreases, which further affects drug distribution. Fat-soluble (nonpolar) drugs readily cross membranes and are taken up by adipose tissue, whereas water-soluble (polar) drugs are confined to lean body tissues. The volume of distribution (V_d) affects the half-life of drugs and duration of drug action. For most fat-soluble drugs such as diazepam, thiopental, lidocaine, and clomethiazole, the V_d increases with aging leading to increases in tissue drug levels and prolonged duration of action.[10-12] Amobarbital[13] and lorazepam[14] are fat-soluble drugs that are exceptions

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Table 1. Summary of Pharmacokinetic Changes With Aging

Absorption	Distribution	Metabolism
↓ Amount of saliva	↓ Cardiac output	↓ Microsomal hepatic oxidation
↑ Gastric pH	↑ Peripheral vascular resistance	↓ Clearance
↓ Gastric acid secretion	↓ Renal blood flow	↑ Steady-state levels
↑ Gastric emptying time	↓ Hepatic blood flow	↑ Half-lives
↓ Gastrointestinal surface area	↓ Body water	↑ Levels of active metabolites
↓ Gastrointestinal motility	↑ Body fat tissue	↓ First-pass metabolism
↓ Active transport mechanism	↑ Volume of distribution for lipid-soluble drugs	
↓ Gastric dopa	↓ Volume of distribution for water-soluble drugs	
↓ Decaboxylase	↓ Serum albumin levels	

Data from Ewing.[3]

to this rule. With regard to water-soluble drugs, there is a decline of distribution with age as shown by cimetidine, digoxin, ethanol, gentamicin, and theophylline,[15–17] with 2 exceptions, eg, pancuronium[18] and tobramycin.[19]

In the elderly, there is a 10% to 20% decrease in plasma albumin concentration.[20] Acidic drugs such as cimetidine and furosemide bind exclusively to albumin, so in the elderly the amount of free fraction of the drug in the circulation increases. The same is true of other highly protein-bound drugs, such as nonsteroidal anti-inflammatory drugs (NSAIDs), oral anticoagulants, phenytoin, and sulfonylureas.[15] It should be noted that, with chronic dosing, free drug[20] concentrations tend to "renormalize" and age-related changes in drug binding may not be as important (particularly with changes in protein binding).[21]

Metabolism

Drug metabolism mainly occurs in the liver[22] and since hepatic blood flow decreases up to 40% in the elderly,[23] there can be a severe reduction in the amount of drug delivered to the liver per unit time. Thus, O'Malley and colleagues[24] have shown that the mean plasma elimination half-life of antipyrine (commonly used as an index of oxidative metabolism) is almost 50% longer in the elderly compared with younger controls. There is an overall tendency for the metabolic activity of older individuals to be less efficient than that of younger individuals. A study of the pharmacokinetic difference between older and younger individuals of the antidepressant nortriptyline, under steady-state conditions, found that patients over the age of 70 years had higher plasma concentrations of this drug even when corrected for dosage and body weight.[25]

Studies of the effect of aging on liver enzymes have shown that drugs subject to oxidative phase I metabolism exhibit decreased elimination, because phase I metabolism is catalyzed by the P450 system in the smooth endoplasmic reticulum of hepatocytes,[5] a process that decreases substantially with age.[8] Phase II hepatic metabolism involves the conjugation of drugs or their metabolites (acetylation, glucuronidation, sulfation, and glycine conjugation) and is generally not age-associated.[8]

Elimination

Renal blood flow delivers drugs or their metabolites to the kidneys for elimination. An important pharmacokinetic change that occurs in persons of advanced age is reduced renal plasma flow, renal tubular clearance, and creatinine clearance.[8] In the kidney, average clearance declines by as much as 50% from age 25 to age 85, despite a serum creatinine level that remains unchanged at approximately 1.0 mg/dL.[8] The following formula is usually used to estimate creatinine clearance in older adults:

$$\mathrm{CrCl} = \frac{[140 - \text{age (years)}] \times \text{lean body weight (kg)}}{72 \times \text{serum creatinine}}.$$

Where lean body weight for males = 50 kg + 2.3 kg/inch for height > 5 feet and for females = 45.5 kg + 2.3 kg/inch for height > 5 feet and multiply the formula for females by 0.85.

Altered renal clearance leads to 2 clinically significant effects: (1) the half-lives of drugs are prolonged, and (2) the serum levels of these drugs are increased.[8] For drugs with a narrow therapeutic index (eg, digoxin, cimetidine, aminoglycosides), serious side effect may occur in older patients if appropriate dose reductions are not made.[8]

PHARMACODYNAMIC CHANGES IN AGING

In the elderly, there is a natural and progressive loss of function of body tissues at the cellular level. These pharmacodynamic changes are especially important in the central nervous system. Movement disorders and forgetfulness are often the result of changes in the level of neurotransmitters rather than neuronal loss; moreover, mental confusion could be due to alterations in cerebral blood flow, which also produce autonomic changes that could result in bradycardia, augmented vasoconstriction in the cold, vulnerability to hypothermia, and other problems with regulation of body temperature. Consumption of excess alcohol often makes these thermoregulatory problems worse.

The altered responses to drugs in the elderly could be due to several factors including age-related changes in drug-receptor interactions, receptor-membrane interactions, post-receptor events, structural changes in organs or tissues, and altered homeostatic functions. The site of action of many drugs is a specific membrane receptor. These include receptors in the adrenergic, cholinergic, and dopaminergic systems, calcium channel antagonism by calcium channel blockers, action by digoxin at the sodium/potassium adenosine triphosphatase (ATPase) site, the gamma aminobutyric acid (GABA) receptor for benzodiazapines, receptors for opioids, anticonvulsants, and some antidepressants.

The most widely studied drug effects are on the β-adrenergic system. Both β-agonists (eg, salbutamol) and β-antagonists

Table 2. Summary of Drugs Affected by Aging

Drug Class	Drugs to be Used With Care	Increased Side Effects	Drug-Drug Interactions
Analgesics	Opoids (higher blood levels in elderly); pentazocine, pethidine, dextropropoxyphene (in co-praxamol)	Nausea, hypotension, CNS effects	
	Nonsteroidal anti-inflammatory (NSAIDs) with long half-lives (piroxicam)	Fluid retention	
Digoxin	Reduce dose in the elderly	Renal excretion is reduced in elderly	
Diuretics	Thiazides—dose should be lowest possible; loop diuretics—dose should be increased	Hyponatremia, postural hypotension, incontinence	With corticosteroids interaction produces hypokalemia; with K-sparing diuretics, hyperkalemia
H_2-antagonists	Higher blood levels in elderly. dose should be lowest possible	Excretion is reduced leading to mental confusion	
Warfarin	Anticoagulant effect increases so begin with small doses	Bleeding	
Angiotensin-converting enzyme (ACE) inhibitors	Small initial doses	Increase risk of renal impairment; hypotension	
β-blockers	Small initial doses. atenolol and sotalol excretion impaired so higher blood levels; propranolol has reduced first-pass metabolism so blood levels increase.	Bradycardia and precipitation of heart failure	With verapamil, quinidine and disopyramide—atrioventricular dissociation and cardiac decompensation
Benzodiazapines	Small doses for the minimum possible period; short half-life drugs are best, eg, lormetazepam		
Phenothiazines	Small doses and regular reviews	Risk of tardive dyskinesia, extrapyramidal effects, anticholinergic effects (urinary retention, constipation); hypothermia in winter.	With metoclopramide, extrapyramidal movements are seen.
Anti-Parkinsonian drugs	Levodopa—small doses; anticholinergic drugs have enhanced effects	Levodopa causes confusion, postural hypotension, psychosis; selegiline causes more agitation and confusion; anticholinergic drugs cause constipation, dry mouth and urine retention	Levodopa with tricyclic antidepressants produce hypertension
Tricyclic antidepressants			With disopyramide and antihistaminics produce hypertension

Data from Ewing.[3]

(eg, propanolol) show decreased responses in the elderly. The total number of β-receptors is not changed in the elderly; rather, it is the postreceptor events that occur after receptor activation that are altered. These altered postreceptor events have been attributed to altered intracellular conditions.[3]

Homeostatic mechanisms that function via central and peripheral feedback mechanisms are altered in the elderly. Postural hypotension often occurs. The baroreflex is blunted, as is the reflex tachycardia that occurs in the upright position. There is increased susceptibility to many commonly used drugs. These include benzodiazapines, antidepressants, neuroleptics, and even NSAIDs, which show an increased penetration into the aged central nervous system. The response of older patients to drugs in general is very variable;

therefore, all drugs should be used appropriately and with caution in these subjects.

DRUG-DRUG INTERACTIONS

Because older people generally use more drugs there is a greater chance for drug interactions. Skoll et al[26] reviewed the prescription of drugs for the elderly in a Saskatchewan Prescription Drug Plan and found that 77.3% of the elderly populace had received at least 1 prescription drug from the Saskatchewan formulary. All subgroups of the elderly (ages 65 to 74, 75 to 84, and 85+) received more prescriptions than their middle-aged counterparts. Such multiplicity could lead to a greater interaction of these multiple drugs as shown in Table 2.

CONCLUSION

In the use of drugs in the elderly, it must be remembered that the current armamentarium of drugs available for the treatment of cardiovascular, metabolic, and other disorders is, for the most part, designed for the younger adult. Therefore, appropriate modifications must be made for the elderly patient—modifications that take into account the altered physiology, pharmacokinetics, and pharmacodynamics that accompany aging. Use of medications in the elderly should be kept to a minimum, with nondrug alternatives considered whenever possible. Drug-drug interactions should be avoided and regular reviews of prescriptions should be undertaken. Whenever possible, therapeutic drug monitoring should be carried out to ensure optimal dosing.

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