Clinical Geriatric Pharmacology

Dong-Ryul Sohn, MD, PhD

Department of Clinical Pharmacology, Soonchunhyang University College of Medicine

The range of disorders of old age that are thought potentially amenable to drug therapy is increasing. However, factors such as the growing costs of drug development and prescription, the novel pharmacological profile and enhanced potency of many new compounds, and the concerns that the elderly may have enhanced susceptibility to toxicity all make drug usage in the eldely patient an increasingly specialized topic. This is compounded by the high incidence of multiple disorders in frail elderly patients, and consequently the possibility of the long term use of several drugs, thus, adding the risk of drug interactions. Thus, clinical pharmacology in the elderly requires understanding of pharmacologic characteristic determinants of the physiological changes (Table 1) associated with aging in terms of pharmacokinetics and pharmacodynamics.

I. Pharmacokinetics in the Elderly

A. Drug absorption

Although the elderly have several alterations in gastrointestinal function, few drugs have delayed absorption or lower extent of absorption. Changes in drug absorption therefore appear to be the least important of age-related changes in the pharmacokinetic factors affecting pharmacologic action of drugs.

B. Drug Distribution in the Elderly

The distribution of a drug in the body depends on body composition, plasma protein binding, and blood flow to the organs. Differences in body composition with aging have been well known, notably a relative decrease in total body water and lean body mass and and an increase in body fat. The volume of distribution of water-soluble drugs in smaller in the elderly, therefore the initial concentrations of those drugs are greater in the elderly than in the young patients. This has been shown in the case of digoxin, antipyrine and cimetidine. In contrast, lipid-soluble drugs tend to have a greater volume of distribution in the elderly because of their increased body fat. Thus, benzodiazepines such as diazepam and nitrazepam with an enlarged volume of distribution may accumulate in the elderly body and therefore may cause their greater incidence of adverse drug reactions.

Previous studies have shown that albumin concentration decreases with aging. Lower levels of albumin may make the elderly more susceptible to the effects of multiple drug therapy on drug binding, making more free drug available for pharmacologic action. However, no convincing evidence appears to exist that increasing age may cause clinically meaningful alterations in the affinity of albumin and other protein (e.g. α_1-acid glycoprotein) for drugs. The combination of decreased albumin concentration and the tendency towards

polypharmacy in the elderly may result in many adverse drug interactions, particularly involving those drugs that are highly protein bound, such as anticoagulants (e.g. warfarin) and oral hypoglycemics (e.g. tolbutamide).

C. Hepatic Drug Metabolism in the Elderly

The clearance of drugs by the liver depends on the activity of the enzymes responsible for biotransformation and on hepatic blood flow. Recent review articles discussing the hepatic drug metabolism in the elderly have concluded that both the metabolism of drugs mediated via hepatic drug-metabolizing enzymes and extraction of drugs dependent on liver blood flow are, in general, less efficient in the elderly than in the young group. With respect to the hepatic metabolism, drugs can be divided grossly into two categories: those with high and low extraction ratios (i.e. flow-limited and enzyme-limited drugs, respectively). The elimination of drugs with a high extraction ratio is dependent on the liver blood flow, which declines with age. Flow-limited elimination occurs following intravenous but not oral administration of such drugs. These drugs undergo an extensive first-pass metabolism when administered orally. On the other hand, the elimination of drugs with a low extraction ratio (e.g. antipyrine, theophylline) depends mainly on the intrinsic metabolic activity of the hepatic drug-metabolizing enzymes. Therefore the effect of age-related change in a physiological parameter such as liver blood flow on the hepatic drug handling depends on the extraction ratio and the mode of administration of that drug.

Antipyrine has been used as a model drug for assessing the hepatic oxidative drug metabolism in the elderly, indicating longer $t_{1/2}$ and decreased clearance in older subjects. It has also been shown that the clearance of antipyrine correlates with liver volume which declines with age. Old age is associated with a reduction in the pre-systemic metabolism of drugs with a high extraction ratio. Thus, the bioavailability of propranolol and labetalol is increased in the elderly. For this reason, other drugs with a high extraction ratio such as metoprolol, verapamil and meperidine should be administered cautiously in the elderly. Although data appear to be incomplete, this would also be the case with poorly extracted or enzyme-limited drugs such as chlordiazepoxide, diazepam, oxazepam, lorazepam, cimetidine, naproxen, theophylline and tolbutamide.

D. Renal Drug Excretion in the Elderly

The best demonstrated alteration in pharmacokinetic disposition of drugs with aging is the reduction on the rate of elimination by the kidneys. Both the glomerular filtration and the tubular secretion rates correlate with the decrease in creatinine clearance (CLcr) that occurs with aging. The rate of CLcr is a useful guide to the rate of renal drug elimination in the elderly, but it can be often difficult to measure in daily clinical practice. However, there are several formulas and nomograms available to estimate CLcr values.

II. Pharmacodynamics in the Elderly

A. Altered Drug Sensitivity in the Elderly

Some examples of age-related alterations in drug sensitivity are given in Table 2. The elderly appear to be sensitive to the effects of benzodiazepine on the central vnervous system: the elderly are sedated at lower concentrations of diazepam than those required in young adults. The elderly are also observed to have an increased sensitivity to nitrazepam. Thus, a dosage reduction of benzodiazepines is recommended in the elderly.

There is firm evidence that the elderly are less responsive to the β-blocking effects of propranolol. It has also been recognized by clinicians for many years that the antihypertensive effect of β-blockers may be somewhat less in the elderly. However, part of this difference between young and elderly hypertensive patients may be due to differences in the pathogenesis of hypertension and renin status. Although plasma propranol steady-state concentrations were significantly higher in the elderly patients, sensitivity to propranolol measured by both reduction in exercise heart rate and the degree of reduction in serum triiodothyronine produced by propranolol was reduced in this group. By relating drug effect to the concentration producing the effect, an index of sensitivity to propranolol may be derived in individual patients. This show a clear age-related decline in sensitivity.

B. Alterations in Physiologic and Homeostatic Mechanisms in the Elderly

The baroreceptor response to changes in blood pressure is decreased and slower in the elderly. However, sympathetic nervous system activity as reflected by the plasma norepinephrine concentration, is increased; basal norepinephrine levels and the increment with standing, cold pressor testing, and exercise are equal or increased in the elderly as compared with young subjects. Although multifactorial in etiology, decreased vasomotor response and increased venous capacitance may be the most important mechanisms of postural hypotension in the elderly. Drugs that alter central nervous system function, sympathetic activity, vasomotor response, cardiac function, or volume regulation may exacerbate postural changes in blood pressure. Phenothiazines, tricyclic antidepressants, levodopa, antihypertensive drugs and diuretics are frequent causes of postural hypotension.

III. Adverse Drug Reactions in the Elderly

Review articles have concluded that the incidence of adverse drug reactions (ADRs) is greater in the elderly than in the young adult patients. The incidence is, however, considered to be underestimated, because ADRs are less readily recognized by the elderly patients and because they may mimic the characteristic signs and symptoms of disease states. Despite the compelling evidence of a greater incidence of ADRs in the elderly, no independent effect of age alone has been shown as a risk factor. Polypharmacy correlated with the incidence of ADRs because old patients are prescribed more drugs than young patients. In addition, the drugs most commonly implicated in the list of ADRs are taken more often by the elderly than by other patients, including digoxin, benzodiazepine, tricyclic antidepressants, non-steroidal antiinflammatory agents, warfarin, diuretics, theophylline, anti-hypertensive and anti-Parkinsonism agents. Adverse effects derived from these drugs are usually dose-related or concentration-related, suggesting that the elderly are more prone to

ADRs as a result of altered pharmacokinetics and pharmacodynamics.

IV. Prescription in the Elderly

Several prescribing strategies have been proposed for the elderly. First, the decision to administer a drug should be made by considering the potential benefits and risks to the elderly patients. Second, the use of fewere drugs at lower doses and in a convenient combination will be able to enhance compliance as well as to decrease possible ADRs. Third, dosage schedule should be kept simple, and multiple-drug regimens be minimized as much as possible. Fourth, medications prescribed should be reviewed regularly. Fifth, when clinical situations and drugs with a low therapeutic index are listed in clical chart of an elderly patient, a more frequent therapeutic drug monitoring is recommended to enhance a therapeutic efficiency. Lastly, it should be remembered that any new symptoms (and/or illness) may be caused by a prescribed drug as well as by an actually new illness in the elderly patient group.

References

손동렬: 노인환자 약물요법의 임상약리학. 대한임상약리학회지 1996; 4: 229-237

Abernethy DR, Azarnoff DL: Pharmacokinetic investigations in elderly patients; clinical and ethical considerations. Clinical Pharmacokinetics 1990; 19: 89-93

Crome P, Flanagan RJ: Pharmacokinetic studies in elderly people. Clinical Pharmacokinetics 1994; 26: 243-247

Feely J, Coakely DC: Altered pharmacodynamics in the elderly. Clinical Geriatric Medicine 1990; 6: 269-283

Greenblatt DJ, Sellers EM, Shader RI: Drug disposition in old age. New England Journal of Medicine 1982; 306: 1081-1088

Parker BM, Cusack BJ, Vestal RE: Pharmacokinetic optimisation of drug therapy in elderly patients. Drugs and Aging 1995; 7: 10-18

Sloan RW: Principles of drug therapy in geriatric patients. American Journal of Family Physician 1992; 45: 2709-2718

Stewart RB, Cooper JW: Polypharmacy in the aged. Drugs and Aging 1994; 4: 449-461

Tumer N, Scarpace PJ, Lowenthan DT: Geriatric pharmacology; basic and clinical consideration. Annual Review of Pharmacology and Toxicology 1992; 32: 271-302

Yuen GJ: Altered pharmacokinetics in the elderly. Clinical Geriatric Medicine 1990; 6: 257-267

Table 1. Physiological changes relevant to clinical pharmacology in the elderly

Pharmacological factors	Age-related physiological changes
Pharmacokinetics	
Absorption	Decreased absorptive surface
	Decreased gastrointestinal blood flow
	Increased gastric pH
	Altered gastrointestinal motility
Distribution	Decreased lean body mass
	Decreased total body water
	Decreased serum albumin concentration
	Increased body fat
Metabolism	Decreased liver mass
	Decreased liver blood flow
	Decreased hepatic drug metabolizing enzyme activity
Excretion	Decreased renal blood flow
	Decreased glomerular filtration rate
	Decreased tubular secretory function
Pharmacodynamics	
Receptor sensitivity	Altered receptor number
	Altered recptor affinity
Cellular transduction	Altered second messenger function
	Altered cellular responses

Table 2. Age-related alterations in drug sensitivity

Cardiovasular	Endocrine
Propranolol	Insulin sensitivity
Verapamil	Cortisol suppression
Furosemide	
Theophylline	Immune/Antihistamine
	Antibody response to vaccination
Central Nervous System	
Benzodiazepines	Respiratory
Halothane	Theophylline
Narcotic analgesics	
Metoclopramide	Anticoagulants
	Warfarin