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Pharmacokinetic-Pharmacodynamic Crisis in the Elderly

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Aging is characterized by a progressive loss of functional capacities of most if not all organs, a reduction in homeostatic mechanisms, and a response to receptor stimulation. Also, loss of water content and an increase of fat content in the body are reported. Therefore, understanding the influence of age-dependent changes in composition and function of the body on the pharmacokinetics and pharmacodynamics of drugs is important before prescribing drugs to elderly patients. In this study, a Medline search for articles published in the period between 1975 and June 2006 was conducted with use of the key words *aging, pharmacokinetics,* and *pharmacodynamics* to review data related to alteration in pharmacokinetics and pharmacodynamics in elderly patients. Analysis of data revealed that the most important pharmacokinetic changes in old age include a decrease in the excretory capacity of the kidney more than the decline in the rate of hepatic drug metabolism. On the other hand, pharmacodynamic changes in the elderly are frequent and commonly ascribed to alteration in the sensitivity to drugs, irrespective of changes in drug disposition. For instance, the sensitivity of the cardiovascular system to β-adrenergic agonists and antagonists decreases in old age, and the incidence of orthostatic episodes in response to drugs that lower blood pressure increases. However, the central nervous system becomes vulnerable in the elderly to agents that affect brain function (eg, opioids, benzodiazepines, and psychotropic drugs). Therefore, these drugs must be used very cautiously in this age group. In conclusion, the complexity of the interactions between polypharmacy, comorbidity, altered pharmacodynamic sensitivity, and even modest changes in pharmacokinetics in elderly necessitate the medical approach "start low and go slow" for aged subjects, especially if drug therapy is considered beneficial or absolutely necessary for them.

Keywords: aging, pharmacokinetics, pharmacodynamics

AGING: GENERAL CONCEPTS

Aging is a complex process that is not very well understood, and there is no universally accepted definition of aging. One acceptable definition is "a progressive unfavorable loss of adaptation of an individual organism as time passes, leading to increased vulnerability, decreased viability, and decreased life expectancy."[1] Also, aging can be functionally defined as a state of failure of maintenance.[2]

Aging affects everything (eg, ethics, economics, society, cells, physiological systems, clinical medicine), including the pharmacokinetics (drug disposition) and pharmacodynamics of drugs.[3] In most industrialized countries, about 15% of the population is older than 65 years, the age that is generally considered the lower limit for defining the elderly. The subjects who are investigated in clinical trials are usually in good health (the fit elderly), and the "real oldies" (>75 years) are very seldom included.[4]

The aim of the present review is to put a spotlight on the alterations in pharmacokinetics and pharmacodynamics of drugs that should be considered when medications are prescribed to the elderly population.

CELLULAR BIOLOGY OF AGING

Body cells have efficient damage control system that protects the cellular components from damage. Age-dependent inhibition of the proteasome and/or lysosomal proteases leads to decline in the proteolytic capacity of the cell, accompanied by an increased accumulation of oxidized proteins.[5] This ultimately

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leads to oxidative damage to bases in genomic and mitochondrial DNA[6] and to redox-sensitive transcription factors such as NFκB and AP1.[7,8] The oxidative stress theory has also been considered as an explanation for changes in cell biology by aging. In vitro studies showed a decline in the cellular defenses against oxidant stress in aging, where the basal rate of lipid peroxidation increases and the ability to scavenge oxygen radicals decreases.[9] In vivo studies demonstrated an increased rate of lipid peroxidation with aging, as measured by pentane exhalation in human subjects.[10] Apoptosis (programmed cell death) also has been proposed as a theory, involving genetically programmed aging through an upregulation process in which every person is programmed by his or her genes to live a certain number of years, and the genes carry instructions not only for growth and development but also for cell destruction. This leads to decline of the body and its death.[11] Brain apoptosis is a good example of age-related neurodegenerative diseases.[12]

AGING, DISEASES, AND DRUGS

Different factors may represent hazards for prescription of drugs to the elderly, such as immobility, multiple diseases, poor fluid intake, poor nutrition, confusion and forgetfulness, inability for self-care, lack of supervision, and poor compliance. Also, altered drug distribution as a result of body composition changes can lead to prolonged half-life or higher plasma concentrations of many drugs. Furthermore, higher prevalence of adverse drug reactions, multidrug regimens, and large interindividual variability in drug response make drug dosage and administration in the elderly challenging. Accordingly, the concept ''crisis of aging'' must be addressed by development of broad expertise and research in geriatric pharmacology to understand and clarify the clinical phenomena most commonly confronting healthcare professionals involved in drug therapy for the elderly.[13–16]

PHARMACOKINETIC CONSIDERATIONS IN AGING

Several physiological changes that might occur with aging have the potential to modify the pharmacokinetics of drugs. The most important physiological changes related to aging that might affect pharmacokinetics of drugs are summarized in table 1.[4,17]

Drug absorption and bioavailability

In elderly patients with intact intestinal mucosa, absorption of drugs usually remains unchanged.[18] Drugs with substantial presystemic elimination (high clearance drugs) may exhibit a variable extent of oral bioavailability in old age. Some drugs such as labetalol, verapamil, nifedipine, and lidocaine exhibit increased oral bioavailability because of decreased intestinal and/or hepatic first- pass metabolism.[19] Other drugs of high clearance, eg, imipramine, amitriptyline, metoprolol, morphine, and pethidine, showed no change in oral bioavailability.[20] Thus, it is difficult to make any generalizations or predictions about intestinal metabolism and its role in aging.

The *MDR1* gene product, P-glycoprotein (P-gp), is an efflux transporter that represents a barrier to drug absorption in the intestine and the transport of various drugs across the blood-brain barrier.[21] The effect of aging on P-gp is controversial. Study of the efflux of the P-gp-probe rhodamine 123 from CD56 (+) natural killer cells with flow cytometry showed no difference in rhodamine fluorescence activity between aged and young subjects.[21] On the contrary, estimation of the activity index of P-gp activity in CD3-positive leukocytes in young and elderly subjects using (R)-[(11)C]verapamil as a substrate for P-gp and positron emission tomography showed decreased P-gp activity during aging; thus, the brain may be exposed to higher drug and toxin levels in elderly subjects.[22]

Drug distribution in aging

Increased fat content and decreased body water with aging may affect the volume of distribution (Vd) of drugs. Hydrophilic drugs such as ethanol, lithium, digoxin, acebutolol, and cimetidine may have a reduced Vd in the elderly and a consequent increase in plasma concentrations. On the other hand, the Vd of liphophilic drugs such as diazepam, antipyrine, and tolbutamide may be increased, and their plasma concentrations may decrease.[14,19,23] Accordingly, loading doses of these drugs may be modified for elderly patients by about 10% to 20%, according to their water or lipid solubility.[13] Another factor that might affect drug distribution is plasma protein binding, which usually decreases in elderly individuals by about 15% to 25% in comparison with nonelderly adults, leading to increased free plasma levels of drugs that have high protein- binding capacity.[24] Although the age-related effects on protein binding have minimal clinical significance drugs with extensive plasma protein binding and high hepatic extraction ratio showed altered Vd if given intravenously to elderly such as propranolol, verapamil, midazolam, lidocaine, doxorubicin and haloperidol.[25,26]

Hepatic metabolism and aging

The age-related reduction in liver size and hepatic blood flow (Table 1) does not markedly affect the liver

function values such as serum albumin, bilirubin, cholesterol, and alkaline phosphatase in older versus young adults.[14] However, these changes may affect hepatic clearance of drugs in elderly subjects, especially in the presence of other cofactors of aging such as frailty, comorbidity, polypharmacy, and smoking.[5,27,28]

Drugs with blood flow-limited metabolism such as propranolol, antipyrine, verapamil, and imipramine display reduced hepatic clearance in old age, which is usually parallel with the fall in hepatic blood flow, whereas the metabolism of drugs with low hepatic extraction ("capacity-limited metabolism") usually is not diminished.[29–31]

A discrepancy has been reported between in vitro and in vivo study findings with regard to the effect of aging on the activity of different cytochrome P-450 enzymes (CYP isoforms) involved in phase I oxidative metabolism of drugs. In vitro studies of hepatic microsomes showed no significant differences in CYP activity and/or inducibility as a function of age.[32,33] On the other hand, in vivo studies showed equivocal results (a decrease or no change) in hepatic drug clearance by different CYP isoforms in the elderly, as shown in Table 2.[17–19,28,29,34–46] The paradoxical pattern of in vitro versus in vivo activity of CYP enzymes in the elderly for phase I drug metabolism may be explained by the oxygen delivery theory: oxygen delivery to liver microsomes is not constrained in the in vitro studies, whereas in the in vivo studies, age-related alterations in the hepatic architecture (such as thickening and defenestration of hepatic sinusoidal endothelium and deposition of collagen) may reduce oxygen availability for phase I drug metabolism.[13,29,47] On the contrary, the enzyme system responsible for metabolism of drugs by conjugation [eg, glucuronidation, sulphation, and acetylation (phase II reaction)] requires oxygen indirectly to produce energy. Therefore, drugs that undergo phase II metabolism may not be affected by reduced oxygen delivery in an aged liver.[48]

One important covariate that may indirectly impair the hepatic drug metabolism in the elderly is the age-related deterioration of renal function through a mechanism of downregulation of the CYP activity by circulating uremic factors induced by renal function deterioration.[49]

Genetic polymorphisms in the CYP enzymes may influence the risk of development of some types of cancers in old age. Males with genetic polymorphism in CYP3A4, especially the G-variant type, had greater susceptibility to prostate cancer with aggressive clinical behavior in old age.[50,51] The coexistence of CYP polymorphisms and aging may accelerate the modulation of drug metabolism. The effect of aging and the CYP2D6*10 polymorphism on the plasma haloperidol concentration after chronic administration of the drug in 110 Japanese patients showed a significant linear correlation between the haloperidol concentration/dose (C/D) ratio and age. The C/D ratio was significantly higher in older subjects than in younger ones, especially in patients with non-CYP 2D6*10 homozygous genotypes versus those with CYP 2D6*10 homozygous genotypes. The study indicated that the effect of age on the haloperidol C/D ratio depends upon the CYP2D6*10 genotype.[52] On the contrary, a study of the influence of age and genotype of the polymorphic enzyme CYP2C9 on the steady-state

Table 1. Physiological changes that occur with aging that can influence the pharmacokinetics of drugs.[4,21]

System	Changes
General	Reduced total body mass, basal metabolic rate, and proportion of body water; increased proportion of body fat
Circulation	Decreased cardiac output; altered relative tissue perfusion; decreased plasma protein binding (?)
Gastrointestinal tract	Reduced gastric acid production, gastric emptying rate, gut motility, gut blood flow, absorption surface, intestinal uptake/transport (?), intestinal metabolism
Liver	Reduced liver mass, blood flow, and albumin synthesis
Kidney	Reduced glomerular filtration rate, tubular function
Lung	Reduced vital capacity

Table 2. Advanced-age-related changes in clearance of some drugs that undergo phase I metabolism by CYP isoforms in humans.[21–23,34,35,40–52]

CYP isoform	Drug substrate	Advanced-age-related effect on drug clearance
CYP1A2	Caffeine-theophylline	No change
CYP2C8/9	Diclofenac-celecoxib	No change
	Ibuprofen-phenytoin	Decreased
CYP2C19	Omeprazole (+ CYP 3A4)	Decreased
CYP 2D6	Amitriptyline-sparteine	No change
CYP 3A4	Midazolam	No change
	Carbamazepine	Decreased
	Resperidone (+ CYP 2D6)	Decreased
	Erythromycin-nifedipine	Decreased
	Lidocaine	Decreased

disposition of diclofenac and celecoxib (anti-inflammatory drugs) revealed no relationship.[53]

Renal drug elimination and aging

The normal kidney loses up to 30% of its weight between the ages of 30 and 90 years, and this is reflected in the loss of 60% or more of glomeruli, accompanied with patchy tubular atrophy, interstitial fibrosis, and arteriosclerosis. Therefore, the glomerular filtration rate (GFR) and renal blood flow are decreased in the elderly, even in the absence of any kidney disease.[54] These physiological changes collectively lead to a steady decrease in creatinine clearance as well as clearance of drugs that are excreted unchanged by the kidney, such as aminoglycosides and vancomycin.[55] Table 3 summarizes the pharmacokinetic data on the aminoglycoside gentamicin in different age groups, with evidence of reduced clearance of both creatinine and gentamicin and prolongation of drug half-life ($T_{1/2}$) with aging.[56–61] The antiviral acyclovir is another example of a drug eliminated primarily by the kidney that may cause renal damage. If given to elderly subjects with expected physiological deterioration of kidney function, acyclovir dosage should be titrated.[62] When renal impairment is associated with other comorbidities with potential influence on renal function in geriatric patients, such as hypertension and diabetes mellitus,[13] potentially toxic levels of drugs commonly prescribed to elderly patients (such as enalapril, cefotaxime, furosemide, spironolactone, hydrochlorothiazide, piracetam, pentoxyfylline, and lorazepam) are expected to be seen, especially because geriatric patients have an estimated creatinine clearance of <40 mL/minute.[62]

PHARMACODYNAMIC CHANGES IN AGING

The aging process may be associated with changes in receptor density and/or affinity, signal transduction mechanisms, and impairment of cellular response in affected organs, resulting from the pathologic state.[63]

Pharmacodynamic changes in both autonomic and central nervous system receptors in association with the aging process are considered here.

Muscarinic acetylcholine receptors play a key role in facilitating cognitive processes in the brain, such that loss of cholinergic function by aging might contribute to the profound learning impairments and memory deficits associated with age-related dementia and Alzheimer's disease.[64] Experimental animal models showed that aging may be associated with reduced expression and/or content of muscarinic cholinergic receptors (M_1 and M_4) in both dorsal (motor) and ventral (limbic) striatum in experimental rats.[65] Colinomimetic drugs such as acetylcholine esterase inhibitors have been found to improve cognitive performance in humans with Alzheimer's disease.[66]

At the cardiac level, the aged heart showed a reduction in number and activity of muscarinic M_2 receptors.[67] This decrease in muscarinic receptor function is consistent with the finding that electrically stimulated release of acetylcholine from atrial tissue decreased with increasing age of the patients.[68]

Adrenergic receptors have a regulatory role in control of cardiovascular activity, and age-related alteration in adrenergic-receptor activity has been specifically observed in relation to cardiovascular responses. Therefore, decline in the baroreceptor reflex buffering of blood pressure by aging has been ascribed at least partly to an age-related reduction in α_1-adrenergic receptor function.[69] This may explain the higher incidence of postural hypotension as a common side effect in elderly patients who are administered nitroglycerine, diuretics, dihydropyridine-type calcium channel blockers (eg, nifedipine and nicardipine), peripheral α_1-blockers (eg, prazosin), and the antipyschotic chlorpromazine.[14] In aged rats, molecular alteration of the G-protein coupling/uncoupling-signaling activity of the α_1-adrenoceptor has been reported. Reduction in the gene expression of α-Gq/11 Gs, responsible

Table 3. Comparative pharmacokinetics of gentamicin in different age groups.

Mean age, years (range)	n	CLcr mL/min/kg	CLp mL/min/kg	Vd L/kg	$T_{1/2}$ hours	Reference no.
33 (4–67)	40	1.57	1.42	0.27	2.2	56
39 (17–55)	30	1.15	1.67	0.35	2.5	57
48 (19–86)	26	1.05	0.77	0.31	4.7	58
55 (19–87)	26	1.39	1.09	0.28	2.8	59
59 (37–82)	27	0.97	1.43	0.30	2.5	60
76 (65–95)	417	0.65	0.74	0.23	5.7	61

CLcr, creatinine clearance; CLp, plasma clearance; Vd, volume of distribution; $T_{1/2}$, half-life.

for protein coupled receptor stimulation, by agonists and an increase in the expression of adrenergic receptor kinase (GRK2) and tyrosine phosphatases (TyrP), responsible for uncoupling of the activated receptor from its G proteins, are likely to explain the age-related decline of vasoconstriction in aged rats.[70] Administration of prazosin, an α_1-adrenoceptor blocker, at a dose of 1.0 mg orally to young and elderly subjects showed no change in its pharmacokinetics between the two age groups. However, it produced a greater decrease in systolic blood pressure and mean blood pressure in elderly versus young subjects. The compensatory increase in heart rate was similar in the two age groups, reflecting a difference in the baroreceptor reflex activity between the two groups.[71]

Animal studies also showed an association between increasing age and reduced activity of cardiac β-adrenoceptors. Although assessment of β-adrenoceptor density in aging myocardium did not yield consistent results (decrease, increase, and no change with aging), a general finding was that coupling of the β-adrenoceptor to the Gs protein and to the catalytic unit of the adenyl cyclase is impaired with aging.[72,73] Alteration in the post-receptor signaling mechanism of β-adrenergic receptors with aging may be responsible for the age-associated reduction in chronotropic and inotropic cardiovascular response to the stimulatory effect of catecholamines on β-adrenergic receptors.[74] It has been proposed that neuronal uptake of catecholamines is reduced in the heart of aged subjects. This may lead to accumulation of noradrenaline neurotransmitter in the synaptic cleft, creating a state of β-adrenoceptor desensitization in cardiac tissue.[67]

The sympathetic nervous system inhibits bladder contraction during the filling phase and maintains normal bladder compliance through β-adrenoceptor (β_3) stimulation.[75] Dysfunction of the bladder is commonly observed in elderly individuals and is partly attributed to age-related alteration in β-adrenoceptor function in detrusor cells of the bladder.[76] Administration of isoprenaline as a nonselective β-adrenergic receptor agonist to elderly patients showed a 15% reduction in detrusor relaxation in response to the drug, suggesting a reduction in β-adrenergic responsiveness in the urinary detrusor cells of elderly subjects to β-adrenergic agonists.[77]

Endogenous opioid peptides have a wide range of physiological and behavioral effects on pain perception, mood, motor control, and autonomic function. In aged subjects, the intensity and/or intrinsic activity of different opioid receptors are changed in a way that affect the response to opioid analgesics.[78] Aged male rats (24 months) and young rats (3 months) have been found equally sensitive to the antinociceptive effects of opioids such as morphine at *Mu* receptors when they are tested at low nociceptive intensity. At higher nociceptive intensity, aged rats have demonstrated more sensitivity than younger rats to the antinociceptive effects of morphine at *Mu* receptors.[79] The δ-opioid receptors located in the cortical and limbic region of the brain may have a modulatory effect on cognitive and emotional functions in elderly.[80] When aged mice were tested for activity of cortical δ-opioid receptors, a dramatic downregulation of these receptors associated with anxiety-like behaviors in mice was observed.[81] Furthermore, mice lacking functional δ-opioid receptors exhibited aggravated depressive-like behaviors.[82] Therefore, it was proposed that age-related impairment of emotionality may, at least in part, result from the dysfunction of cortical δ-opioid receptors during the aging process.[82]

Benzodiazepine pharmacodynamics showed alteration in elderly versus young patients. Patients with advanced age showed increased sensitivity to the central nervous system effects of benzodiazepines such as diazepam[74] and midazolam.[83] Also, a dissociation has been reported between pharmacodynamics and pharmacokinetics of many of benzodiazepines in the elderly, and the age-related increase in sensitivity to the clinical effects of benzodiazepines such as sedation, memory, and psychomotor impairment were not accounted for by differences in benzodiazepine blood concentrations.[84] Age-related reasons for this dissociation may include a slower rate of tolerance development, higher brain concentrations due to alterations in blood-brain barrier permeability, an increase in benzodiazepine receptor binding, an increase in receptor functionality, and/or a decrease in homeostatic reserve, which all may develop with aging.[85]

CLINICAL APPLICATIONS

It is difficult to review all the progress made to date regarding alterations in drug pharmacokinetics and pharmacodynamics associated with aging. Here we highlight some of the drugs commonly used in elderly patients.

Cardiovascular drugs

Digoxin

As patients age, congestive heart failure becomes an increasingly important problem, and it accounts for up to 20% of hospital admissions for patients older than 65 years.[86] Digoxin is recommended for patients with heart failure due to left ventricular systolic dysfunction who are not adequately responsive to angiotensin

converting enzyme inhibitors and diuretics and for those with atrial fibrillation and rapid ventricular rates.[87] The drug has been shown to reduce morbidity and to improve quality of life by reducing symptoms and preventing hospitalizations for heart failure.[88]

The age-related increase in adipose tissue and decline in total body water/lean body mass result in reduction of the Vd of digoxin in elderly patients. As a result, the loading dose should be reduced by approximately 20%. Digoxin is cleared mainly by glomerular filtration in the kidney, and a decreased glomerular filtration rate with aging may lead to decreased clearance of the drug and thus its accumulation. Therefore, therapeutic drug monitoring of digoxin is advisable in the elderly, especially when drug administration is associated with impaired kidney function. This will be greatly helpful in optimization of the maintenance dose.[89]

The recommended therapeutic range for serum digoxin concentration is 0.5 to 2 ng/mL. Under normal circumstances, no patient exhibits signs or symptoms of digoxin toxicity when the serum drug concentration is 1.4 ng/mL or less. On the other hand, patients with a digoxin level >3 ng/mL showed evidence of digitalis toxicity. However, clinical evidence of digoxin toxicity in patients more than 70 years old increased despite a decrease in the serum digoxin level to between 1.4 and 2 ng/mL.[90] This overlapping between serum digoxin level and increased incidence of digitalis toxicity in aged patients reflects a tendency toward greater sensitivity of cardiac tissue in the elderly to digoxin. This may probably be ascribed to increased sensitivity of Na^+-K^+ ATPase and/or decreased sarcolemal content of that enzyme, causing reduced reserve capacity of sodium pumps in cardiac tissue. In addition, susceptibility to potassium loss due to diuretics and reduced renal function in the elderly put these patients at greater risk for digitalis toxicity.[91]

Verapamil

Verapamil is a calcium channel blocker characterized by high protein binding and extensive first-pass metabolism, which both can affect its plasma concentration. The drug is widely used in the elderly for treatment of hypertension, cardiac arrhythmia, and ischemic heart disease. Plasma clearance of the drug in aged subjects showed a tendency to be reduced and its plasma concentration to be increased.[92] In spite of this, elderly patients demonstrated reduced dromotropic activity (sensitivity of L-type calcium channels) to verapamil, as evident by reduced prolongation of the cardiac P-R interval.[93,94] These changes were more apparent in elderly patients with rheumatoid arthritis who were administered verapamil to control a concurrent cardiac problem (Figure 1).[95] In the figure, an increase in the area under the plasma concentration-time curve (AUC) of S-verapamil in elderly patients with rheumatoid arthritis reflects increased serum concentration of the drug, associated with reduced clearance. The pharmacokinetic alteration was also associated with changes in verapamil pharmacodynamics, as evidenced by reduction in the cardiac dromotropic response to the drug. The proinflammatory mediators have been suggested to reduce activity and function of cardiac calcium channels through a downregulation and/or inactivation of channels.[96,97]

Warfarin

In the elderly population, atrial fibrillation represents a large and growing epidemic associated with increased risk of stroke as a complication. Therefore, warfarin anticoagulation is considered effective in reducing this risk.[98] Warfarin has a narrow therapeutic index and high interindividual variability in dose requirement, which make its use in the elderly challenging. Study of the pharmacokinetics of warfarin in young versus elderly subjects showed no significant difference.[14] However, altered warfarin pharmacodynamics in the elderly have been reported; increased sensitivity to the anticoagulant effect of warfarin, secondary to greater inhibition of synthesis of vitamin K-dependent clotting factors, was noted at similar plasma concentrations in elderly versus young patients.[74] Also, the dose-adjusted prothrombin time ratio (PTR) and dose-adjusted international normalized ratio (INR) have been found to increase with age.[99] Therefore, older patients may require a lower starting dose (2.5 to 5.0 mg) of warfarin than younger patients (7.5 to 10 mg).[100] It is important to mention here that genetic polymorphisms of CYP 2C9 enzyme responsible for hepatic metabolism of warfarin have no influence on variability of response to the drug in nonelderly adult versus elderly populations.[101]

Drugs of the central nervous system

Morphine

Perioperative control of pain in elderly subjects is a critical issue in anesthetic practice because older patients facing surgery may have systemic diseases (eg cardiac, pulmonary, endocrine) that are usually associated with advanced stage. Elderly subjects administered morphine for pain control showed a tendency for reduced clearance (Figure 2),[102] increased vulnerability to adverse drug effects, and reduced rate of development of tolerance.[103] This may explain why dose

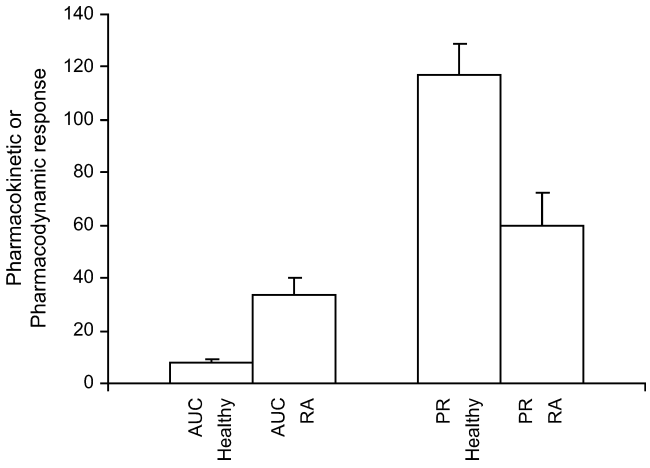

FIGURE 1. Area under serum S-verapamil concentration-time curves (AUC, mg/L^{-1} • min) and the area under percent cardiac P-R interval prolongation (from baseline, %Xh) following administration of 80 mg racemic verapamil to healthy volunteers and patients with rheumatoid arthritis (RA). Error bars represent standard error of the mean (n = 8/group).[95]

escalation of opioids such as morphine in older patients is significantly lower than in younger patients.[104,105]

Psychotropic drugs

Hallucinations and/or delusions are common psychotic disorders in elderly subjects.[106] They may be caused by a primary psychotic disease (eg, schizophrenia) or psychosis secondary to dementia, as observed in Alzheimer's disease, Lewy body dementia, or Parkinson's disease.[107] Conventional antipsychotics (eg, chlorpromazine and haloperidol) and atypical antipsychotics (eg, clozapine, risperidone, and quetiapine) are used to control these psychotic disorders. In elderly subjects, conventional antipsychotics cause adverse effects (eg, extrapyramidal symptoms, tardive dyskinesia, and anticholinergic symptoms) more than atypical antipsychotics,[108] even at similar effective therapeutic doses.[109] Atypical antipsychotics also have distinct therapeutic advantages over conventional antipsychotics in improvement of negative symptoms of psychosis such as depression and hostility and better efficacy in addressing the positive symptoms of psychosis such as hallucinations and delusions.[110,111] Risperidone, as an atypical antipsychotic, has achieved better control of psychotic symptoms at a lower dose (<1 mg/day) in elderly subjects.[112] However, a similar dosage of the drug was found to achieve higher plasma concentrations in elderly subjects than in young patients (Figure 3); this was attributed to age-related physiological changes such as decreased hepatic metabolism and reduced renal glomerular filtration rate. Therefore, close monitoring of the plasma concentration of the drug and its metabolite, 9-hydroxy risperidone, is recommended for elderly patients, to avoid dose-related adverse effects.[113] Also, elderly patients with dementia who are maintained on risperidone treatment should be monitored closely for possible cerebrovascular adverse

	Young	Elderly
Age [years]	23-28	60-69
CL [l/kg/h]	2.02 ± 0.30	1.66 ± 0.46 ($p<0.05$)
Vd_{ss} [l/kg]	2.12 ± 0.50	1.16 ± 0.53 ($p<0.05$)

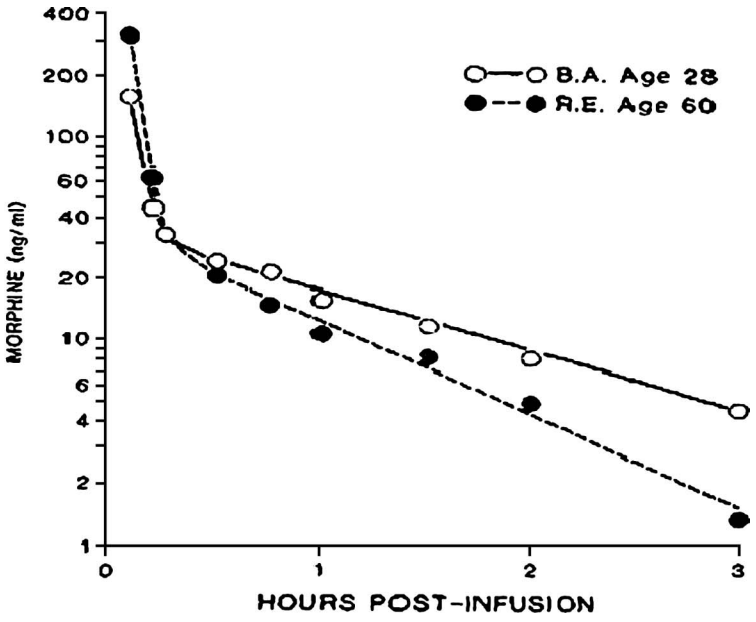

FIGURE 2. Morphine pharmacokinetics (young vs. elderly individuals). CL, clearance; Vdss, steady state volume of distribution.[102]

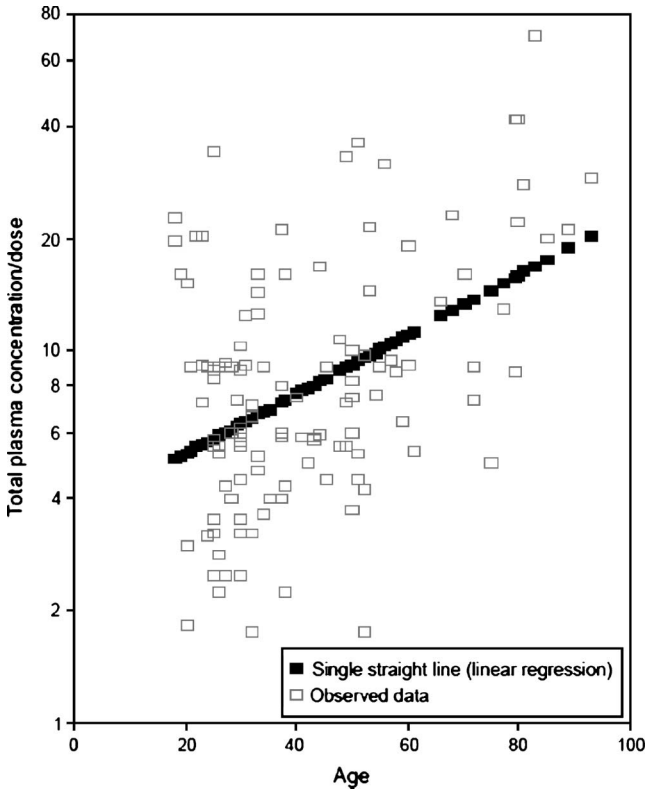

FIGURE 3. Age-dependent C/D (total plasma concentration/dose) ratio ($R^2 = 0.196$, $P < 0.001$); 20.2% increase per 10 years.[113]

effects associated recently with the drug in this category of patients.[110,115]

PATTERN OF DRUG USE IN THE ELDERLY

The broad aims of medical drug usage in the elderly population are improving morbidity and prolonging survival without any adverse effects on quality of life. Inappropriate use of medications in the elderly may involve prescription of expensive drugs, incorrect directions for use, no definite indication, and over dosage of drugs that carry a risk of adverse drug reactions, including interactions.[116] Another serious problem is underutilization of appropriate medications such as statin therapy. Statin drugs have been found to be associated with reduced mortality in all age groups, especially very elderly individuals suffering from significant coronary artery disease. In spite of this, the prescription and utilization of these drugs for elderly patients have been found to be significantly lower than for younger patients (<65 years, 28.0%; 65–79 years, 21.1%; and ≥80 years, 19.8%).[117,118]

CONCLUSIONS

The aging process is characterized by structural and functional changes that affect all body systems and result in reduced homeostatic capacity. This creates a state of "failure of maintenance" and "loss of adaptation" of body organs as time passes.

Changes in body composition and in hepatic and renal function may be responsible for altered pharmacokinetics in aging, such as reduced clearance, prolonged elimination half-life, and increased volume of distribution, particularly of lipid-soluble drugs.

Increased sensitivity to drugs with aging is attributed to commonly altered pharmacodynamics, which may not be related to pharmacokinetic changes. The impairment of receptor intensity and/or affinity as well as post-receptor signaling mechanisms that occurs with aging may be responsible. Also, age-related reduction of functional reserve in the form of impaired homeostatic compensatory mechanisms may participate in altered pharmacodynamics. Finally, better understanding of the effects of aging would enhance the quality of drug prescription for older patients.

REFERENCES

1. Liew CC. Biochemical aspects of aging. In: Gornall AG, ed. *Applied Biochemistry of Clinical Disorders*. 2nd ed. Philadelphia: Lippincott Raven Press; 1986:558–565.
2. Rattan SI. Aging: a biological perspective. *Mol Aspects Med*. 1995;16:439–508.
3. Greengross S, Murphy E, Quam L, et al. Aging: a subject that must be at top of world agendas. *BMJ*. 1997;315:1029–1030.
4. Crome P, Flanagan RJ. Pharmacokinetic studies in elderly people: are they necessary? *Clin Pharmacokinet*. 1994;26:243–247.
5. Grune T, Merker K, Jung T, et al. Protein oxidation and degradation during postmitotic senescence. *Free Radic Biol Med*. 2005;39:1208–1215.
6. Richter C. Oxidative damage to mitochondrial-DNA and its relationship to aging. *Int J Biochem Cell B*. 1995;27:647–653.
7. Kim H-J, Chung H-Y. Molecular exploration of age-related NFκB/IKK downregulation by calorie restriction in rat kidney. *Free Rad Biol Med*. 2002;32:991–1005.
8. Kim HJ, Jung KJ, Seo AY, et al. Calorie restriction modulates redox-sensitive AP-1 during the aging process. *J Am Aging Assoc*. 2002;25:123–130.
9. Sitte N, Merker K, Grune T, et al. Lipofuscin accumulation in proliferating fibroblasts *in vitro*: an indicator of oxidative stress. *Exp Gerontol*. 2001;36:475–486.
10. Zarling EJ, Mobarhan S, Bowan P. Pulmonary pentane excretion increases with age in healthy subjects. *Mech Aging Dev*. 1993;67:141–147.
11. Higami Y, Shimokawa I. Apoptosis in the aging process. *Cell Tissue Res*. 2002;301:125–132.

12. Anglade P, Vyas S, Hirsch EC, et al. Apoptosis in dopaminergic neurons of the human substantia nigra during normal aging. *Histol Histopathol*. 1997;12:603–610.
13. McLean AJ, Le Couteur DG. Aging, biology, and geriatric clinical pharmacology. *Pharmacol Rev.* 2004;56:163–184.
14. Hammerlein A, Derendorf H, Lowenthal DT. Pharmacokinetic and pharmacodynamic changes in the elderly: clinical implications. *Clin Pharmacokinet*. 1998;35:49–64.
15. Abrams WB, Beers MH. Clinical pharmacology in an aging population. *Clin Pharmacol Ther.* 1998;63:281–284.
16. Flammiger A, Maibach H. Drug dosage in the elderly: dermatological drugs. *Drugs Aging*. 2006;23:203–215.
17. Herrlinger C, Klotz U. Drug metabolism and drug interactions in the elderly. *Best Pract Res Clin Gastroenterol*. 2001;15:897–918.
18. Klotz U. Effect of aging on the pharmacokinetics of gastrointestinal drugs. In: Pilotto A, Malfertheiner P, Holt PR, eds. *Aging and the Gastrointestinal Tract*. Vol. 32. Basel: Interdiscipl Top Gerontol, Karger; 2003:28–39.
19. Turnheim K. Drug dosage in the elderly. Is it rational? *Drugs Aging*. 1998;13:357–379.
20. Wilkinson GR. The effects of diet, aging, and disease-states on presystemic elimination and oral drug bioavailability in humans. *Adv Drug Deliv Rev.* 1997;27:129–159.
21. Brenner SS, Klotz U. P-glycoprotein function in the elderly. *Eur J Clin Pharmacol*. 2004;60:97–102.
22. Toornvliet R, van Berckel BN, Luurtsema G, et al. Effect of age on functional P-glycoprotein in the blood-brain barrier measured by use of (R)-[(11)C]verapamil and positron emission tomography. *Clin Pharmacol Ther.* 2006; 79:540–548.
23. Klotz U, Avant GR, Hoyumpa A, et al. The effect of age and liver disease on the disposition and elimination of diazepam in adult man. *J Clin Invest*. 1975;55:347–59.
24. Schmucker DL. Liver function and phase I drug metabolism in the elderly. *Drugs Aging*. 2001;18:837–851.
25. Grandison MK, Boudinot FD. Age-related changes in protein binding of drugs: implications for therapy. *Clin Pharmacokinet*. 2000;38:271–290.
26. Benet LZ, Hoener BA. Changes in plasma protein binding have little clinical relevance. *Clin Pharmacol Ther.* 2002;71:115–21.
27. Kitani K. Hepatic drug metabolism in the elderly. *Hepatology.* 1986;6:316–319.
28. Kinirons MT, Crome P. Clinical pharmacokinetic considerations in the elderly: an update. *Clin Pharmacokinet*. 1997;33:302–312.
29. LeCouteur DG, McLean AJ. The aging liver. Drug clearance and oxygen diffusion hypothesis. *Clin Pharmacokinet*. 1998;34:359–373.
30. Turnheim K. When drug therapy gets old: pharmacokinetics and pharmacodynamics in the elderly. *Exp Gerontol*. 2003;38:843–853.
31. Wynne H. Drug metabolism and ageing. *J Br Menopause Soc*. 2005;11:51–56.
32. Shimada T, Yamazaki H, Mimura M, et al. Interindividual variations in human liver cytochrome P-450 enzymes involved in the oxidation of drugs, carcinogens and toxic chemicals: studies with liver microsomes of 30 Japanese and 30 Caucasians. *J Pharmacol Exp Ther*. 1994; 270:414–423.
33. Parkinson A, Mudra DR, Johnson C, et al. The effects of gender, age, ethnicity, and liver cirrhosis on cytochrome P450 enzyme activity in human liver microsomes and inducibility in cultured human hepatocytes. *Toxicol Appl Pharmacol*. 2004;199:193–209.
34. Ogura C, Kishimoto A, Mizukawa R, et al. Age differences in effects on blood pressure, flicker fusion frequency, salivation and pharmacokinetics of single oral doses of dothiepin and amitriptyline. *Eur J Clin Pharmacol*. 1983;25: 811–814.
35. Greenblatt DJ, Abernethy DR, Matlis R, et al. Absorption and disposition of ibuprofen in the elderly. *Arthritis Rheum*. 1984;27:1066–1069.
36. Randolph WC, Seaman JJ, Dickson B, et al. The effect of age on theophylline clearance in normal subjects. *Br J Clin Pharmacol*. 1986;22:603–605.
37. Durnas C, Loi CM, Cusack BJ. Hepatic drug metabolism and ageing. *Clin Pharmacokinet*. 1990;19:359–389.
38. Tassaneeyakul W, Veronese ME, Birkett DJ. Co-regulation of phenytoin and tolbutamide metabolism in humans. *Br J Clin Pharmacol*. 1992;34:494–498.
39. George J, Byth K, Farrell GC. Age but not gender selectively affects expression of individual cytochrome P450 proteins in human liver. *Biochem Pharmacol*. 1995;50:727–730.
40. Tanaka E. In vivo age-related changes in hepatic drug-oxidizing capacity in humans. *J Clin Pharm Ther*. 1998;23: 247–255.
41. Simon T, Becquemont L, Hamon B, et al. Variability of cytochrome P450 1A2 activity over time in young and elderly healthy volunteers. *Br J Clin Pharmacol*. 2001;52: 601–604.
42. Battino D, Croci D, Rossini A, et al. Serum carbamazepine concentrations in elderly patients: a case-matched pharmacokinetic evaluation based on therapeutic drug monitoring data. *Epilepsia*. 2003;44:923–929.
43. Bebia Z, Buch SC, Wilson JW, et al. Bioequivalence revisited: influence of age and sex on CYP enzymes. *Clin Pharmacol Ther.* 2004;76:618–627.
44. Gorski JC, Vannaprasaht S, Hamman MA, et al. The effect of age, sex, and rifampin administration on intestinal and hepatic cytochrome P450 3A activity. *Clin Pharmacol Ther.* 2003;74:275–87; erratum, 2004;75:249.
45. Aichhorn W, Weiss U, Marksteiner J, et al. Influence of age and gender on risperidone plasma concentration. *J Psychopharmacol*. 2005;19:395–401.
46. Ishizawa Y, Yasui-Furukori N, Takahata T, et al. The effect of aging on the relationship between the cytochrome P450 2C19 genotype and omeprazole pharmacokinetics. *Clin Pharmacokinet*. 2005;44:1179–1189.
47. McLean AJ, Morgan DJ. Clinical pharmacokinetics in patients with liver disease. *Clin Pharmacokinet*. 1991;21: 42–69.
48. Wynne HA, Cope LH, Herd B, et al. The association of age and frailty with paracetamol conjugation in man. *Age Ageing*. 1990;19:419–424.

49. Shah RR. Drug development and use in the elderly: search for the right dose and dosing regimen (Parts I and II). *Br J Clin Pharmacol*. 2004;58:452–469.
50. Paris OL, Kupelian PA, Hall JM, et al. Association between a CYP3A4 genetic variant and clinical presentation in African-American prostate cancer patients. *Cancer Epidemiol Biomarkers Prev*. 1999;8:901–905.
51. Bangsi D, Zhou J, Sun Y, et al. Impact of a genetic variant in CYP3A4 on risk and clinical presentation of prostate cancer among white and African-American men. *Urol Oncol*. 2006;24:21–27.
52. Ohara K, Tanabu S, Ishibashi K, et al. Effects of age and the CYP2D6*10 allele on the plasma haloperidol concentration/dose ratio. *Prog Neuropsychopharmacol Biol Psychiatry*. 2003;27:347–350.
53. Brenner SS, Herrlinger C, Dilger K, et al. Influence of age and cytochrome P450 2C9 genotype on the steady-state disposition of diclofenac and celecoxib. *Clin Pharmacokinet*. 2003;42:283–292.
54. Muhlberg W, Platt D. Age-dependent changes of the kidneys: pharmacological implications. *Gerontology*. 1999;45: 243–253.
55. Morike K, Schwab M, Klotz U. Use of aminoglycosides in Elderly patients. Pharmacokinetic and clinical considerations. *Drugs Aging*. 1997;10:259–277.
56. Hoey LL, Tschida SJ, Rotschafer JC, et al. Wide variation in single, daily-dose aminoglycoside pharmacokinetics in patients with burn injuries. *J Burn Care Rehabil*. 1997; 18:116–124.
57. Lackner TE, Birge S. Accuracy of pharmacokinetic dose determination of gentamicin in geriatric patients. *DICP*. 1990;24:29–32.
58. el-Sayed YM. Correlation between nephrotoxicity and pharmacokinetic parameters of gentamicin. *J Clin Pharm Ther*. 1994;19:267–271.
59. Peterson AK, Duffull SB. Population analysis of once-daily dosing of gentamicin in patients with neutropenia. *Aust N Z J Med*. 1998;28:311–315.
60. Ordovas JP, Ronchera CL, Poveda JL, et al. Selection of optimal prophylactic aminoglycoside dosage in cancer patients: population pharmacokinetic approaches. *J Clin Pharm Ther*. 1994;19:47–56.
61. Zaske DE, Irvine P, Strand LM, et al. Wide interpatient variations in gentamicin dose requirements for geriatric patients. *JAMA*. 1982;248:3122–3126.
62. Muhlberg W, Platt D. Age-dependent changes of the kidneys: pharmacological implications. *Gerontology*. 1999;45: 243–253.
63. Feely J, Coakley D. Altered pharmacodynamics in the elderly. *Clin Geriatr Med*. 1990;6:269–283.
64. Zhang X. Cholinergic activity and amyloid precursor protein processing in aging and Alzheimer's disease. *Curr Drug Targets CNS Neurol Disord*. 2004;3:137–152.
65. Tayebati SK, Di Tullio MA, et al. Age-related changes of muscarinic cholinergic receptor subtypes in the striatum of Fisher 344 rats. *Exp Gerontol*. 2004;39:217–223.
66. Clader JW, Wang Y. Muscarinic receptor agonists and antagonists in the treatment of Alzheimer's disease. *Curr Pharm Des*. 2005;11:3353–3361.
67. Brodde OE, Leineweber K. Autonomic receptor systems in the failing and aging human heart: similarities and differences. *Eur J Pharmacol*. 2004;500:167–176.
68. Oberhauser V, Schwertfeger E, Rutz T, et al. Acetylcholine release in human heart atrium: influence of muscarinic autoreceptors, diabetes and age. *Circulation*. 2001;103:1638–1643.
69. Jones PP, Christou DD, Jordan J, et al. Baroreflex buffering is reduced with age in healthy men. *Circulation*. 2003;107:1770–1774.
70. Passmore JC, Joshua IG, Rowell PP, et al. Reduced alpha adrenergic mediated contraction of renal preglomerular blood vessels as a function of gender and aging. *J Cell Biochem*. 2005;96:672–681.
71. Andros E, Detmar-Hanna D, Suteparuk S, et al. The effect of aging on the pharmacokinetics and pharmacodynamics of prazosin. *Eur J Clin Pharmacol*. 1996;50:41–46.
72. Ferrara N, Davia K, Abete P, et al. Alterations in β-adrenoceptor mechanisms in the aging heart. Relationship with heart failure, aging. *Clin Exp Res*. 1997;9: 391–403.
73. Roth DA, White CD, Podolin DA, et al. Alterations in myocardial signal transduction due to aging and chronic dynamic exercise. *J Appl Physiol*. 1998;84:177–184.
74. Mangoni AA, Jackson SHD. Age-related changes in pharmacokinetics and pharmacodynamics: basic principles and practical applications. *Br J Clin Pharmacol*. 2003; 56:254–260.
75. Igawa Y, Yamazaki Y, Takeda H, et al. Functional and molecular or biological evidence for a possible β3-adrenoceptor in the human detrusor muscle. *Br J Pharmacol*. 1999;126:819–825.
76. Madersbacher S, Pycha A, Schatzl G, et al. The aging lower urinary tract: a comparative urodynamic study of men and women. *Urology*. 1998;51:206–212.
77. Li G, Li K, Li Z, et al. Age-dependent changes in β-adrenoceptor function in human detrusors and possible mechanisms. *Chin Med J (Engl)*. 2003;116:1511–1514.
78. Narita M, Funada M, Suzuki T. Regulations of opioid dependence by opioid receptor types. *Pharmacol Ther*. 2001;89:1–15.
79. Smith MA, Gray JD. Age-related differences in sensitivity to the antinociceptive effects of opioids in male rats: influence of nociceptive intensity and intrinsic efficacy at the mu receptor. *Psychopharmacology*. 2001;156:445–453.
80. Meltzer CC, Smith G, DeKosky ST, et al. Serotonin in aging, late-life depression, and Alzheimer's disease: the emerging role of functional imaging. *Neuropsychopharmacology*. 1998;18:407–430.
81. Narita M, Kuzumaki N, Narita M, et al. Age-related emotionality is associated with cortical delta-opioid receptor dysfunction-dependent astrogliosis. *Neuroscience*. 2006;137:1359–1367.
82. Filliol D, Ghozland S, Chluba J, et al. Mice deficient for delta- and mu-opioid receptors exhibit opposing

alterations of emotional responses. *Nat Genet*. 2000;25: 195–200.
83. Klotz U. Effect of age on pharmacokinetics and pharmacodynamics in man. *Int J Clin Pharmacol Ther*. 1998;36:581–585.
84. Bertz RJ, Kroboth PD, Kroboth FJ, et al. Alprazolam in young and elderly men: sensitivity and tolerance to psychomotor, sedative, and memory effects. *J Pharmacol Exp Ther*. 1997;281:1317–1329.
85. Platten HP, Schweizer E, Dilger K, et al. Pharmacokinetics and the pharmacodynamic action of midazolam in young and elderly patients under tooth extraction. *Clin Pharmacol Ther*. 1998;63:552–560.
86. Boxer R, Yang SX, Hager WD. Congestive heart failure and the elderly. *Conn Med*. 2003;67:497–503.
87. Aronow WS, Frishman WH, Cheng-Lai A. Cardiovascular drug therapy in the elderly. *Heart Dis*. 2000;2:151–167.
88. Haji SA, Movahed A. Update on digoxin therapy in congestive heart failure. *Am Fam Phys*. 2000;62:409–416.
89. Hanratty CG, McGlinchey P, Johnston GD, et al. Differential pharmacokinetics of digoxin in elderly patients. *Drugs Aging*. 2000;17:353–362.
90. Miura T, Kojima R, Sugiura Y, et al. Effect of aging on the incidence of digoxin toxicity. *Ann Pharmacother*. 2000;34: 427–432.
91. Moore A, Mangoni AA, Lyons D, et al. The cardiovascular system in the aging patient. *Br J Clin Pharmacol*. 2003;56:254–260.
92. Cotreau MM, von Moltke LL, Greenblatt DJ. The influence of age and sex on the clearance of cytochrome P450 3A substrates. *Clin Pharmacokinet*. 2005;44:33–60.
93. Abernethy DR, Schwartz JB, Todd EL, et al. Verapamil pharmacodynamics and disposition in young and elderly hypertensive patients altered electrocardiographic and hypotensive responses. *Ann Intern Med*. 1986;105:329–336.
94. Abernethy DR, Wainer IW, Longstreth JA, et al. Stereoselective verapamil disposition and dynamics in aging during racemic verapamil administration. *J Pharmacol Exp Ther*. 1993;266:904–911.
95. Mayo P, Skeith K, Russell AS, et al. Increased S-verapamil plasma concentration in rheumatic arthritis without increased cardiac effect. *Br J Clin Pharmacol*. 2000;50: 605–613.
96. Lui SJ, Zhou W, Kennedy RH. Suppression of β-adrenergic responsiveness of L-type Ca^{2+} current by IL-1β in rat ventricular myocytes. *Am J Physiol*. 1999;276:H141–H148.
97. Kulmatycki KM, Jamali F. Drug disease interactions: role of inflammatory mediators in disease and variability in drug response. *J Pharm Pharm Sci*. 2005;8:602–625.
98. Cooper HA. Trials of newer approaches to anticoagulation in atrial fibrillation. *J Interv Card Electrophysiol*. 2004; 10(Suppl 1):27–31.
99. Casner PR, Sandoval E. Increased sensitivity to warfarin in elderly Hispanics. *J Clin Pharmacol*. 2002;42:145–150.
100. Squizzato A, Steidl L, Ageno W. Current issues in the initial phase of warfarin therapy. *Recent Prog Med*. 2005; 96:612–615.
101. Siguret V, Gouin I, Golmard JL, et al. Cytochrome P450 2C9 polymorphisms (CYP2C9) and warfarin maintenance dose in elderly patients. *Rev Med Interne*. 2004;25:271–274.
102. Owen JA, Sitar DS, Berger L, et al. Age-related morphine kinetics. *Clin Pharmacol Ther*. 1983;34:364–368.
103. Wilder-Smith OH. Opioid use in the elderly. *Eur J Pain*. 2005;9:137–140.
104. Buntin-Mushock C, Phillip L, Moriyama K, et al. Age-dependent opioid escalation in chronic pain patients. *Anesth Analg*. 2005;100:1740–1745.
105. Wang Y, Mitchell J, Moriyama K, et al. Age-dependent morphine tolerance development in the rat. *Anesth Analg*. 2005;100:1733–1739.
106. Mintzer J, Targum SD. Psychosis in elderly patients: classification and pharmacotherapy. *Psychiatry Neurol*. 2003;16:199–206.
107. Jeste DV, Twamley EW. Understanding and managing psychosis in late life. *Psychiatric Times*. 2003; XX. Available at www.psychiatrictimes.com (accessed July 12, 2006).
108. Finkel S. Pharmacology of antipsychotics in the elderly: a focus on atypicals. *J Am Geriatr Soc*. 2004;52:S258–S265.
109. van Iersel MB, Zuidema SU, Koopmans RT, et al. Antipsychotics for behavioural and psychological problems in elderly people with dementia: a systematic review of adverse events. *Drugs Aging*. 2005;22:845–858.
110. Kirkwood CK, Givone DM. Advances in pharmacotherapy of psychotic disorders in the elderly. *Consult Pharm*. 2003;18:539–550.
111. Taylor M, Turner M, Watt L, et al. Atypical antipsychotics in the real world: a naturalistic comparative outcome study. *Scott Med J*. 2005;50:102–106.
112. Brodaty H, Ames D, Snowdon J, et al. A randomized placebo-controlled trial of risperidone for the treatment of aggression, agitation, and psychosis of dementia. *J Clin Psychiatry*. 2003;64:134–143.
113. Aichhorn W, Weiss U, Marksteiner J, et al. Influence of age and gender on risperidone plasma concentrations. *J Psychopharmacol*. 2005;19:395–401.
114. Bianchetti A, Ranieri P, Margiotta A, et al. Pharmacological treatment of Alzheimer's Disease. *Aging Clin Exp Res*. 2006;18:158–162.
115. Bianchetti A, Ranieri P, Margiotta A, et al. Pharmacological treatment of Alzheimer's Disease. *Aging Clin Exp Res*. 2006;18:158–162.
116. Hanlon JT, Artz MB, Pieper CF, et al. Inappropriate medication use among frail elderly inpatients. *Ann Pharmacother*. 2004;38:9–14.
117. Majumdar SR, Gurwitz JH, Soumerai SB. Undertreatment of hyperlipidemia in the secondary prevention of coronary artery disease. *J General Intern Med*. 1999;14:711–717.
118. Allen Maycock CA, Muhlestein JB, Horne BD, et al. Intermountain Heart Collaborative Study. Statin therapy is associated with reduced mortality across all age groups of individuals with significant coronary disease, including very elderly patients. *J Am Coll Cardiol*. 2002; 40:1777–1785.