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Geriatric pharmacology

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With the demographic change that has resulted in a "graying of the population" has come a compelling interest in the health concerns of older adults. The increasing incidence and prevalence of systemic diseases, especially chronic diseases, among older adults, and the concomitant increase in medication use, have provided impetus for the subspecialty of geriatric pharmacology. Although it has long been obvious that because children are smaller than adults some reduction of drug dosage is appropriate, it was not understood until recently how elderly patients differ from younger adults. In fact, there were some widely held misconceptions about aging, as, for example, that senility or a progressive increase in blood pressure are normal concomitants of aging. Geriatric pharmacology did not emerge out of a specific incident, such as occurred with thalidomide, in which it was made clear that the fetus represents an area of special concern for the pharmacologist. Rather, the field of geriatric pharmacology has developed out of changes in demography that have been accompanied by an increasing knowledge of and sensitivity to the special physiologic, pharmacologic, pathologic, psychologic, economic, and emotional concerns of older adults.

In 1999, elderly persons 65 years of age or older numbered 34.5 million and represented 12.7% of the US population; by the year 2030, they will represent 20% and will number approximately 70 million [1]. Furthermore, not only is the total over-65 group growing faster than the population as a whole, but between the years 2000 and 2030 the group aged 85 years and older will increase from 4.3 million to 7 million [2,3].

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Of special interest to the dentist is that the newer cohorts of older adults are now and will be in better oral health [4]. The rate of edentulousness has declined [5–7], and the number of retained teeth among the dentate has increased [5,6,8,9]. With this trend among dentate older adults has emerged an understanding that there are similar needs for routine restorative and periodontal treatments among these individuals as exist among younger adults [6,8,10]. Accordingly, an increasing number of elderly people will need the kind of dental treatment that was formerly rare in the elderly patient, treatment that requires among other things antianxiety drugs, analgesics, local anesthetics, and anti-inflammatory drugs. It also means that the dentist will be confronted by an increasing number of ambulatory, community-dwelling elderly patients with a significant burden of systemic disease and medication use.

Normative aging studies have shown that the healthy elderly person is substantially and measurably different from younger counterparts. More recently, pharmacologists have begun to appreciate how these changes affect the pharmacokinetics and pharmacodynamics of drugs.

As people age, they are more likely to present to the dental office with a variety of diseases, especially chronic diseases, for which they take many drugs that are strong in effect and potentially toxic. Americans aged 65 years and older take a disproportionately high percentage of all drugs prescribed [11]. Furthermore, studies of ambulatory populations indicate that although 80–90% of older adults take at least one medication, most are taking two or more. The most commonly used drugs are agents affecting the cardiovascular system, analgesic and anti-inflammatory drugs, psychotherapeutic medications, and gastrointestinal preparations such as laxatives and antacids. Approximately 40% of medications are prescribed to patients to be taken "as necessary," with an average of three drugs per patient [12].

Multiple medications prescribed to individuals of any age increases the risk for adverse drug reactions, drug interactions, and other health-related problems associated with the use and misuse of medications [12,13]. The potential problems in older adults are compounded by the potential age-related physiologic changes that may place these individuals at greater risk. The misuse of medications by elderly patients is considered a major healthcare problem [14,15]. Finally, many segments of our society, not the least important of which is the healthcare provider, have become sensitized to the nonmedical problems common among the elderly (loneliness, depression, poverty, poor nutritional status) and have come to understand how these can complicate therapeutic management of elderly patients.

This article presents a view of geriatric pharmacology that deals mainly with alterations in drug responsiveness that can be attributed directly to aging, and deals only in passing with those psychosocial factors that indirectly have an impact on how elderly patients use and react to drugs.

Physiologic changes associated with aging

Studies of the aging process in community-dwelling, healthy (presumed disease-free) individuals have provided insights into the process of biologic aging. These studies have been either cross-sectional studies, in which different-aged persons are assessed at the same point in time, or longitudinal studies, in which the same individuals are assessed at different times as they "age in place." Although the former studies are easier and quicker to complete, they limit inferences to "age differences" rather than "age-related changes," because of the limitations in controlling for and measuring individual differences in biology and behavior. Results of cross-sectional and longitudinal studies have reported a gradual decline in performance from the third decade through the seventh and eighth decades in a broad range of physiologic functions, including renal function, pulmonary function, cardiac function, and nerve conduction velocity [16]. Findings from these studies have shown, however, that (1) there are broad individual intersubject differences in the rate of aging, (2) not all organ systems age at the same rate, (3) the pattern of age-related declines in organ systems can vary among individuals, (4) with increasing age, there is greater variability among individuals within an age cohort in measures of organ functioning, (5) age-associated declines are greater in more complex integrative functions (such as maximum breathing capacity) than in basic functions (such as the velocity of propagation of a nerve impulse along a nerve), and (6) the latency and capacity for achieving adaptive responses are, respectively, greater and smaller for older individuals than younger individuals. Thus, variability is a cardinal feature of the aging process. It has also been suggested that at least some of the apparent decline in functioning may reflect changes in lifestyle rather than chronologic aging per se (such as declining muscle mass associated with the adaptation of a more quiescent life-style).

Age-related changes in drug disposition that have potential importance to drug use are summarized in Table 1. These alterations affect the absorption, distribution, biotransformation, and excretion of drugs; the specific features of these changes are considered later. There also is a well-documented decline in homeostatic competence in elderly patients that accounts for the increased incidence of postural hypotension with age [17], the increasing sluggishness of thermoregulation, and the fact that the elderly are less able to compensate rapidly for the hypotensive effects, for instance, of an antihypertensive drug [18]. Elderly patients undergo physiologic changes that could be characterized as normal concomitants of the aging process, but that they also, to a greater or lesser extent, suffer changes that are disease- and medication-related. Because what we consider aging represents an interplay among the physiology of aging, disease, and the cumulative effects of behavioral and lifestyle choices (eg, sedentary living and tobacco use versus regular exercise and abstention from tobacco), the elderly population is more heterogeneous than, for instance, a population of children between birth and puberty [19].

Table 1
Summary of age-related changes that affect drug disposition in older adults

Pharmacokinetic property	Physiologic change	Possible influence on drug effect
Absorption	↑ Gastric pH	Increased absorption of drugs inactivated by stomach acid
	↓ Absorptive surface	Minor effect
	↓ Splanchnic blood flow	Minor effect
	↓ Gastrointestinal motility	Minor effect
Distribution	↓ Cardiac output	Impaired delivery of drugs to organs of elimination
	↓ Total body water	Increased concentration and effect of drugs distributed in body water
	↓ Lean body mass	Increased concentration and effect of drugs distributed in lean body mass
	↓ Plasma albumin	Increased effect of, and interaction between, drugs extensively bound to albumin
	↑ α_1-Acid glycoprotein	Minor effect
	↑ Body fat	Increased sequestration of lipophilic drugs in fat
Metabolism	↓ Hepatic mass and enzyme activity	Decrease phase I metabolism of some drugs
	↓ Hepatic blood flow	Decreased metabolism of drugs normally rapidly cleared by the liver
Excretion	↓ Renal blood flow	Decreased renal elimination of water-soluble drugs and metabolites
	↓ Glomerular filtration rate	Decreased renal excretion of water-soluble drugs and metabolites
	↓ Tubular secretion	Decreased renal elimination of drugs and metabolites actively secreted into urine

Nonphysiologic aspects of aging

Multiple disease states

Elderly people suffer from more health problems, especially chronic diseases and conditions, than younger people. The most prevalent chronic conditions among older adults are listed in Table 2. Some of these diseases are degenerative (eg, cataracts, detached retina), others are caused by

Table 2
Prevalence of selected reported chronic illnesses[a]

Condition	Prevalence by age (yr)		
	65–74	>75	All ages
Arthritis	444.7	550.4	129.9
Hypertension	372.6	373.6	121.5
Hearing impairment	273.7	380.7	90.8
Heart disease	271.8	333.6	84.1
Chronic sinusitis	176.2	167.8	139.7
Cataract formation	118.1	246.0	25.3
Deformity or orthopedic impairment	151.4	176.6	111.6
Diabetes	95.2	87.8	25.8
Visual impairment	67.4	127.6	34.7
Tinnitus	89.4	75.1	26.4

[a] Prevalence data (number of cases/1000 persons) from Adams PF, Hardy AM. Current estimates from the National Health Interview Survey, 1988. Vital and Health Statistics, Series 10, No. 173. Hyattsville (MD): US Department of Health and Human Services, Public Health Service, Centers of Disease Control, National Center for Health Statistics; 1989.

cumulative exposure to environmental contaminants (eg, cases of chronic obstructive pulmonary disease and cancer), and still others are the consequences of essentially normal processes of aging (eg, decreased bone density with increasing age). Among older adults there is an increased incidence of all varieties of heart disease (arrhythmias, myocardial infarction, valvular disease), renal disease, atherosclerosis, arthritis, diabetes, osteoporosis, a variety of gastrointestinal problems, declines in humoral- and cell-mediated immune responses (that lead to a decreased resistance to infectious diseases), and various sensory and musculoskeletal impairments. It has been estimated that more than four out of five persons aged 65 years and older have at least one chronic illness, and multiple coexisting conditions are commonplace among older adults. The leading chronic health conditions for this age group are arthritis, hypertensive disease, and heart disease [20,21].

It is not surprising that although the elderly represent less than 13% of the population, they account for 30% of hospitalizations [22] and 32% of drug use [23]. It also is noteworthy that symptoms of disease in older adults often present differently than in younger individuals. For example, infections are sometimes manifested not by fever but by tachycardia in older individuals. Furthermore, transient or episodic symptoms may be forgotten, misreported, or misinterpreted.

Numerous studies have shown that older adults, because of a higher prevalence of chronic disease, are the principal consumers of drugs [11,24]. The use of over-the-counter (OTC) with prescription medications for the treatment of chronic diseases in older adults has dual implications. These agents can provide a cure or palliative treatment of a disease in a nontoxic and economical manner. Because of the age-related changes in physiologic status

and age-dependent and age-related diseases, however [25], medications can induce adverse reactions that can be a major source of morbidity or even mortality [13,26].

Adverse drug reactions

The incidence of adverse drug reactions among older adults is much greater than among younger individuals, and this increase is related for the most part to polypharmacy (multiple drug use). Important factors in the occurrence of adverse drug reactions, however, are multiple diseases (especially chronic diseases), hepatic or renal insufficiency, small body size, malnutrition, and previous drug reactions. Important adverse reactions include side effects (eg, dry mouth with tricyclic antidepressant medication), drug allergy (eg, pruritus or hives), and toxic reactions [27] (eg, digitalis toxicity). Toxic reactions are especially important in older adults and may be caused by a broad range of potential pharmacodynamic changes (age-related changes in drug sensitivity) or pharmacokinetic changes (including decreased renal function and changes in lean body mass and water content).

Adverse drug reactions can be categorized into two principal groups: unexpected and unpredictable versus predictable and preventable. An unexpected, unpredictable reaction is an unwanted consequence of drug administration that occurs at appropriate doses for prophylaxis, diagnosis, or therapy. Examples of such reactions include allergic responses, idiosyncratic reactions, or secondary pharmacologic effects. In contrast, predictable, preventable drug reactions involve an unwanted consequence of drug administration that occurs because of failure in decision making by the healthcare provider. Failure by the dentist to choose the appropriate agent can occur, as in prescribing the wrong drug for a disease or prescribing a drug with known potential adverse effects in a susceptible patient.

Because most adverse drug reactions are preventable, it is important to understand the patient's medical history, drug history, and current list of medications (OTC and prescribed), the pharmacology of each agent used, and any abnormal physiologic factors that can affect drug action. Although the incidence of adverse reactions increases among older patients, in part because of polypharmacy, actions of a single powerful agent can produce severe adverse reactions for the elderly patient. Many of the drugs commonly prescribed by dentists can produce a variety of harmful reactions in their patients. As illustrated in Table 3, a variety of drug classes used in dental practice can be of potential risk for the older patient. For example, cephalosporins commonly prescribed for the treatment of infections can produce deleterious effects. Cefoperazone, cefamandole, and cefotetan can prolong prothrombin time and partial thromboplastin time, which can impair hemostasis [28,29]. Other antibiotics, such as clindamycin, can markedly increase the incidence of such gastrointestinal problems as diarrhea and colitis in patients older than 60 years of age [30,31]. In addition to antibiotics,

Table 3
Age-related increased risk of toxicity with some commonly prescribed dental agents

Drug	Increased risk for elderly patients
Clindamycin	Diarrhea and colitis
Metronidazole	Toxic plasma concentrations (patients over 70 years of age)
Cephalosporins	Impaired clotting mechanisms and bleeding problems
NSAIDs[a]	Compromised renal or gastrointestinal function
Opioid analgesics	Increased plasma half-life, respiratory depression
Glucocorticoids	Muscle wasting and osteoporosis with chronic therapy
Benzodiazepines	Impaired memory and decrements in psychomotor performance

[a] NSAIDs, nonsteroidal anti-inflammatory drugs.

nonsteroidal anti-inflammatory drugs (NSAIDs) also can cause morbidity in the elderly population. The NSAIDs are commonly used for postoperative pain control in dental practice; however, NSAID use among older adults can be a problem, as documented by an association of NSAID intake with impaired renal function, GI toxicity, or hypertension [32–34]. Therefore, alternatives to NSAIDs can include the use of COX-2 inhibitors such as celecoxib and rofecoxib. More specifically, because NSAIDs inhibit the COX-1 and COX-2 pathways, the use of selective COX-2 inhibitors provides anti-inflammatory and analgesic properties with less GI toxicity [35].

Another dilemma encountered by older adults that complicates the dental treatment plan is medications that may cause xerostomia. Drug-induced xerostomia is a concern because (1) older adults take prescription and nonprescription medications at a higher rate than the general population, (2) there are many medications that have xerostomic potential (more than 400 medications have been implicated), and (3) the oral health sequelae of xerostomia are consequential. Xerostomia induced by sympathomimetics, diuretics, anticholinergics, tricyclic antidepressants, antihistamines, antiparkinson drugs, psychotropic agents, cardiovascular agents, and muscle relaxants can greatly impair oral health and function [36]. Potential sequelae of xerostomia include rampant dental caries, periodontal problems, difficulty in speech and swallowing, mouth soreness, impaired denture retention, greater likelihood of oral infection, and altered sense of taste [37,38].

Polypharmacy is a special attribute of drug use among older adults. One fourth of hospitalized patients over age 65 receive six or more drugs daily [39], older adults average 13 prescriptions per year [40], and approximately 90% of patients aged 75 years and older take drugs regularly, with greater than one third taking three or more drugs daily [41]. The major consequence of multiple drug use is an increased incidence of adverse drug reactions. These adverse drug reactions result from several factors, including incorrect identification of medications, multiple prescriptions from more than one health provider (because of a lack of awareness or communication among providers), and the use of medications prescribed for someone else.

Because most adverse drug reactions are preventable, dentists should take advantage of available resources to minimize the likelihood of these untoward sequelae. Consultation with other health professionals (including physicians and pharmacists) or use of a comprehensive drug reference book assists in determining the appropriate drug and dose schedule. In addition, computer-based data retrieval systems and newsletters can keep the dentist informed regarding appropriate drug selection. Finally, the dentist should always be aware of and concerned about the onset of new symptoms that do not normally arise from the anticipated course of the disease process but do follow from dental treatment.

The salient point to remember concerning adverse drug reactions in older adults is that they are largely preventable. A sound approach to avoid adverse drug reactions involves (1) understanding the physical and psychosocial changes that occur in older adults, (2) knowing the pharmacokinetics and pharmacodynamics of the medications the patient is taking and ones the dentist is planning to use or prescribe, (3) evaluating the existing prescription drug burden of an individual when considering further prescription needs, (4) prudent drug monitoring, and (5) careful record keeping.

Patient compliance

Patient compliance can be a major source of medication errors. Ample evidence exists that a substantial percentage of elderly patients make serious or potentially serious medication errors [42]. Failure to comply with drug regimens consists of omitting medications, use of medications not prescribed by the physician or dentist, and errors of dosage, sequence, and timing. Problems especially identified with the elderly that contribute to compliance errors include poor comprehension and memory, deficits in vision and hearing, financial strictures, inability to cope with the environment, self-neglect, cultural attitudes, and physical obstacles to getting medications out of the bottle (particularly the child-resistant kind) and self-administering them. Therefore, whenever possible unnecessary medications should be eliminated, and drugs with simplified dosing schedules should be selected. Prescription strategies by the dentist, including written instructions, use of drugs that require fewer doses per day (eg, doxycycline instead of tetracycline), selection of less expensive generic alternatives, and packaging of drugs in easy-open, daily dosing boxes increase the likelihood of compliance.

Psychosocial factors

Any discussion of geriatric pharmacology would be incomplete without mention of the various psychosocial and economic challenges that frequently confront the elderly. Although it is no longer true that older adults inevitably suffer a serious reduction in income, 10.5% live in poverty, and elderly single women (14% are below the poverty line) are worse off than men or couples. Furthermore, poverty rates are higher for elderly Blacks

(25%) and Hispanics (24%) than for elderly Whites (9%) [43]. The elderly may also live in increasing isolation, away from families, children, and spouses, and suffer from depression, loneliness, and sometimes senility. They also receive three times as many prescriptions for psychotropic drugs as do younger people, even though they are more vulnerable to the adverse effects of these drugs and take twice as long to recover from them than do young patients [44]. This constellation of factors places older adults at risk for many problems, including inadequate diet, poor nutrition, loss of weight, forgetfulness and inattention to medical and pharmacologic needs, and an inability or lack of desire to fill prescriptions and to take them as directed. One widely held belief about the elderly is that their nutritional status is compounded by losses in salivary secretory ability and taste acuity that are presumed to occur with aging and would naturally interfere with the enjoyment of food. Although some studies showed a decrease in parotid gland secretion and salivary amylase activity, and morphologic age-related changes in the salivary gland, most studies have not found a diminution of salivary flow in older individuals [45,46], and the decline in gustatory function is at most modest among the elderly [47]. It cannot be denied that pathologic aging may have an adverse effect on salivary function, however, and that many of the drugs and treatments to which the older person is subject can cause xerostomia of varying degrees of severity.

Pharmacologic changes associated with aging

Two basic mechanisms have been developed to explain age-related differences in drug effects [27]. The pharmacodynamic mechanism suggests that changes in drug responsiveness account for such differences [48,49]. These changes presumably involve either an alteration in the number or activity of receptors on the target cell or a change in intracellular responses to receptor activation. Documentation in support of this mechanism is modest, involving only a few drug classes. The more widely accepted pharmacokinetic mechanism suggests that age differences in drug response are related to changes in drug disposition as a result of alterations in drug absorption, distribution, metabolism, and excretion or combinations of these processes. A general review of these factors with particular regard to aging is provided in the following sections.

Pharmacokinetics of drugs

Absorption

Most medications prescribed to patients living independently are taken orally. These medications are absorbed through the gastrointestinal tract. The documented age-related alterations that might predispose older adults to potential declines in absorption are increased gastric pH, decreased

absorptive surface, decreased gastric emptying, decreased splanchnic blood flow, and impaired intestinal motility [50,51]. There is little evidence, however, to support an age-related decline in absorption [49]. In fact, it is possible that decreased stomach acidity could improve absorption of drugs normally inactivated by stomach acid. An important consideration for patients of all ages is the possible interaction of medications with food. For example, the absence of food in the gastrointestinal tract improves the efficiency of absorption of some drugs, such as erythromycin. The absorption of other medications is unimpaired, however [27]. Thus, although food–drug interactions are not a problem of aging per se, they are important in older adults who have a heavier medication burden.

Distribution

The distribution of the drug to potential receptor sites occurs after absorption of the drug through the gastrointestinal tract and then into the bloodstream. Distribution is influenced by body composition (lean body mass, body water, and adipose tissue mass), plasma protein binding (particularly albumin), and blood flow to organs. The documented age-related changes that might affect drug distribution in older patients include decreased lean body mass, decreased body water, increased body fat, decreased cardiac output, and decreased albumin [51].

The change in lean body mass may reflect other factors, including a potential lifestyle change in physical activity or dietary change, rather than an aging effect per se; nevertheless, this consistent finding in older adults must be considered when evaluating the patient. The net effect is a decrease in lean body mass and total body water, and an increase in total body fat. Thus, the respective volumes of distribution for water-soluble medications and fat-soluble medications are decreased and increased, respectively [51]. Water-soluble drugs such as acetaminophen, ethanol, digoxin, and cimetidine are distributed in a smaller volume in older individuals and, therefore, have higher concentrations at the same dose [49,51]. Similarly, the more lipid-soluble drugs such as diazepam are more widely distributed (yielding a lower concentration at the receptor site) and have a longer terminal half-life in older adults [49,51].

Although decreased plasma titers of albumin are probably not a concomitant of aging, they may accompany chronic disease seen in an aging population. A decrease in plasma albumin increases the availability of highly bound drug, thereby effectively increasing the drug concentration at the receptor. A higher concentration of free drug in the plasma has been shown for salicylic acid, metronidazole [52], and phenytoin, but not for warfarin [53]. Theoretically at least, therapeutic and toxic effects should be achieved at lower blood concentrations for drugs that are extensively protein-bound [54]. This effect may be especially important with malnutrition. Furthermore, for many drugs there has been no documented age-related difference in protein binding; two examples are diazepam and penicillin G [55].

Metabolism

The metabolism of most drugs begins with the obligatory passage through the liver after absorption from the gastrointestinal tract. Hepatic metabolism depends on hepatic blood flow, the liver enzymes responsible for biotransformation of the drug, and genetic factors that influence the hepatic enzyme system [27,51]. The reported age-related declines that might be responsible for altered drug disposition include decreased liver mass and decreased hepatic blood flow [51]. It has been suggested that biologic variability, drug use, and behavioral factors (such as smoking or alcohol use), or a combination of these factors, exert a greater effect than age on hepatic metabolism.

The documented age-related effects may impair the efficiency of the phase I pathways of metabolism, namely, oxidation, reduction, and hydrolysis. The phase II pathways of glucuronidation, acetylation, and sulfation are unaffected [51]. For drugs that are rapidly cleared by the liver, the rate-limiting step in biotransformation is the hepatic blood flow. Thus, the metabolism of high-clearance drugs such a propranolol is reduced, and caution should be exercised with regard to the tricyclic antidepressant and antiarrhythmic medications. For low-clearance drugs, metabolism depends on the efficiency of the hepatic enzyme systems. Thus, some benzodiazepines (such as desmethyldiazepam) that depend on microsomal oxidation have a prolonged half-life, whereas others (such as lorazepam) that undergo conjugation are unaffected by age. It is also important to consider the route of administration when assessing the potential for hepatic metabolism. The preceding discussion presumes the oral route of administration that involves the absorption of the drug from the gastrointestinal tract and then transport through the liver by way of the hepatic portal circulation; however, the parenteral route of administration may eliminate the liver as the organ primarily influencing disposition of the drug.

Excretion

The elimination of drugs by the kidney provides the eventual pathway for removal of most medications. The documented age-related changes that might impair kidney function and excretion include decreased renal blood flow, decreased glomerular filtration rate, and decreased tubular secretion [51]. Renal function is typically evaluated by the creatinine clearance that has been reported to decline by approximately one third between the ages of 20 and 90 years in the ambulatory, community-dwelling volunteers of the Baltimore Longitudinal Study on Aging [56]. More recent data from the same study, however, have shown that for approximately one third of older subjects, renal function did not decline, and further, there were variable declines among other older subjects [57]. These latter data underscore the need to establish adequate dosing schedules for medications based on blood concentrations rather than interpretation of age-adjusted ''normative'' data.

Drugs that are eliminated primarily unchanged in the kidney include digoxin, gentamicin, amantadine, lithium, nadolol, and lisinopril. Dosages for drugs with a high therapeutic index, such as penicillins and cephalosporins, are usually not adjusted for older adults (in the absence of renal disease or polypharmacy). It is important to adjust dosages for medications with active metabolites, such as the benzodiazepines diazepam and flurazepam [49].

The response of elderly patients to drugs is affected not only by alterations in renal drug clearance but by the fact that altered renal function may make them more sensitive to the nephrotoxicity of such drugs as the NSAIDs and aminoglycosides. Conversely, the decreased activity of the renin-angiotensin system may blunt the effects of drugs that inhibit renin secretion, such as β-adrenergic blocking agents and the angiotensin-converting enzyme inhibitors, diminishing their therapeutic effectiveness in the treatment of hypertension [58].

The complex and potentially serious alterations in kidney function mandate that consideration be given to renal excretory capacity when prescribing drugs to the elderly. Although there is certainly a diminution in renal function that is related to age, kidney disease is, of course, not restricted to the elderly.

Pharmacodynamic changes

Studies investigating age-related changes in pharmacodynamics are difficult to pursue, and consequently scant data exist in this area. Available evidence suggests that there are no global age-related changes in drug sensitivity. Increased sensitivity to certain benzodiazepine anxiolytic medications and decreased sensitivity to β-adrenergic agonists and antagonists have been reported in older individuals.

There are several possibilities for pharmacodynamic alterations in drug reactivity with aging, including a change in the number of receptors, a change in their affinity for the drug, or a change in tissue responsiveness to drug-receptor binding. Discovering which of these possibilities accounts for a particular reaction is difficult because it requires a knowledge of receptor number, binding affinity, and quantitation of the sequential steps following the drug-receptor interaction to the final observed response. Experimental evidence exists that one or more of these changes do occur with several groups of drugs, but interpretation of the results of some of these experiments is confounded by the fact that the elderly also demonstrate decreases in homeostatic competence, speed of performance, thermoregulation, and immunocompetence.

Changes in sensitivity to β-adrenergic agonists and antagonists have been reported in several studies. Using the production of cyclic 3′-5′ adenosine monophosphate (cAMP) by lymphocytes as an indicator of responsiveness to isoproterenol in the young and old, it was found that there is a decrease in adenylate cyclase in normal subjects of ages 67 to 90 as compared with those of 18 to 27 years of age [59]. Sensitivity of young men to isoproterenol

and propranolol was demonstrated to be greater than in elderly men, but it is possible that the well-documented increase in the blood concentration of norepinephrine in the elderly may create competition for receptor sites [60]. In a recent series of investigations involving rat myocardial and human lymphocytic β-adrenergic function, a decreased responsiveness of the β receptors to catecholamines was found along with decreased adenylate cyclase activity but no decline in receptor density [61].

Increased sensitivity to central nervous system depressants is a recognized fact. In tests involving nitrazepam, age-related decrements in psychomotor performance were described and linked to pharmacodynamic, not pharmacokinetic, changes [62]. Elderly patients who were given diazepam for a surgical procedure required lower doses than younger patients to reach the same level of sedation [63]. This observation has been confirmed in other studies for diazepam and temazepam [64]. Determination of the minimum alveolar concentration for isoflurane showed an 18% decrease in anesthetic requirement between young adults and older adults; similar results have been obtained with other anesthetics [65]. In contrast to the generalization that brain function in the elderly seems to be inherently more susceptible to disruption by anesthetic drugs, the greater sensitivity of older patients to etomidate seems to result from a decreased initial distribution of the anesthetic after intravenous injection [66].

In addition to pharmacodynamic changes, the genetic characteristics of an individual may also influence the behavior of drugs in the elderly. For example, the apparent volume distribution of the acetylator phenotype of isoniazid decreased significantly with age [67]. Hence, pharmacogenetics for the elderly is important because genetically determined enhancement or impairment of drug action in the body can amplify toxicity of a drug or diminish the efficacy of a drug.

Precautions for the dental practitioner

It should be clear that the elderly patient differs from the younger adult in ways that have the potential for affecting responses to drugs. Changes potentially affecting pharmacokinetics and pharmacodynamics occur during aging, but at this stage in the development of the science of geriatric pharmacology, there are remarkably few documented instances of problems with drugs that arise directly out of these changes. It is, however, well known that responses to drugs in the elderly are confounded by multiple medications, pathologic states, compliance errors, and a variety of psychologic, sociologic, and economic difficulties that beset older people. Some precautions appropriate to dentistry are listed below.

1. The elderly usually take more drugs, prescription and nonprescription, than the general adult population, and drug interactions and adverse drug reactions are more likely to result from polypharmacy. It is

important, therefore, that the dentist take a careful history of the patient's medical and pharmacologic status and update it at regular intervals during treatment.

2. Older adults are more sensitive than are young adults to the depressant effects of drugs. It may be necessary to reduce the dosages of analgesics, antianxiety drugs, sedative-hypnotics, and general anesthetics.
3. Because of the known decline in homeostatic competence, drugs that alter blood pressure, heart rate, and smooth muscle tone should be used with caution in the elderly. Conversely, immunosenescence may dictate more aggressive antibiotic therapy than normal for the prevention and treatment of infections.
4. Older adults are more susceptible to orthostatic hypotension than are younger adults. Dentists must be especially attentive when older adults are transferred from a reclining posture in the dental chair to a standing position.
5. Age-associated decline in renal function is common in otherwise healthy elderly patients, and this decline in function is compounded in patients with kidney disease. This fact should be taken into consideration when prescribing drugs whose principal route of elimination is the kidney. Conventionally, dosage intervals are increased in such circumstances, but the dose of the drug or drugs may have to be reduced.
6. The dentist should be aware of the psychosocial and economic considerations for the patient and should be sensitive to such problems as the expense of the medications and the possibility of forgetfulness and poor compliance. Special packaging, clear labeling, and simplified dose regimens may improve compliance, as may having a responsible relative or friend monitor drug therapy.

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