Special Considerations for Geriatric Therapeutic Drug Monitoring

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Numerous physiological changes during the normal aging process can potentially affect how drugs are handled by the body. Gastrointestinal changes include increased gastric pH, decreased intestinal motility, and decreased blood perfusion. Age-related changes in body composition and protein concentrations in plasma contribute to alterations in the distribution of drugs. Hepatic metabolism of drugs may be affected, and renal excretion via glomerular filtration or tubular secretion is diminished. The importance of each of these physiological changes in the elderly, as well as the contribution of multi-drug therapy and other external factors, is discussed.

A review of the demographics of the developed countries demonstrates that most of us are living within a population whose mean age is on the increase. The last census revealed that the group of individuals older than 65 years constituted >11% of the U.S. population. More significant is the fact that this percentage will double in the near future. Three major factors are contributing to this trend. First is the fact that average longevity has grown significantly over the last half century. Second, the aging of the large segment of the population represented by the "baby boomers" of the 1950s will have a major effect on the mean age of the overall population, as well as on the demand for health-care delivery. A third factor is the general downward trend in the birth rate, which also contributes to unbalancing the age distribution of the population.

Although the elderly make up about one-ninth of the U.S. population, they account for a significantly larger share of the overall national health expenditures. They occupy a large share of beds in hospitals and other care facilities, usually as a consequence of chronic or long-term health concerns, and consume a disproportionate share (approximately 30%) of prescribed drugs (1). This statistic is supported by studies showing drug consumption by as many as 66% of elderly patients (2, 3). A significant fraction of the geriatric population are receiving multi-drug therapy (2, 4, 5). In some studies nearly half of the elderly study group received at least three separate medications per day. Thus it is not surprising that adverse drug reactions are frequent in elderly patients. As many as 10% of the hospital admissions involving older persons result from adverse reactions to a prescribed drug (6, 7), many of which appear to be a consequence of multiple drug therapy.

Until the "Fountain of Youth" is discovered, each of us is subject to becoming a future "senior citizen," and must face the fact that the aging human body becomes increasingly susceptible to the disease processes and physiological changes that accompany old age. Fortunately, a multitude of drugs are available to correct, or at least moderate, the effects of many disease states. To optimally prescribe and use therapeutic agents in the geriatric population, it is important to understand the factors that affect the pharmaco-kinetics and pharmacodynamics of these drugs. In the following discussion, I will address the physiological and biochemical changes that coincide with the normal aging process and indicate how these changes may affect both the dosing and monitoring of drugs used in the geriatric population.

Drug Absorption

Prescribed drugs are most commonly given orally and the majority of these drugs are absorbed in the small intestine by way of passive diffusion. Thus any factors that might affect both the rate and degree of contact with the intestinal mucosal surface may produce significant changes in the drug-absorption profile.

The gastric emptying rate will directly influence drug absorption. Although there is conflicting evidence as to whether there are changes in gastric emptying time attributable to the aging process alone (8-10), numerous external factors affect gastric emptying, including diet, disease states, stress, concurrent drug therapy, pain, emotional state, body position, and gastric pH.

The elderly exhibit a higher incidence of reduced gastric acid secretion (11, 12), which has been associated with a delay in gastric emptying. While certain drugs are present in the stomach, the pH of the gastric fluid may have an effect on their stability as well as their absorption pattern. For example, drug formulations that require exposure to an acidic environment for maximal dissolution may demonstrate reduced absorption in the presence of low amounts of gastric acid. Other drugs, which display less stability in acidic conditions, may degrade in the acidic environment of the stomach if gastric emptying is delayed. For some special formulations such as enteric-coated tablets, absorption may be altered as a result of delayed gastric emptying. Decreases in gastric emptying rate will be important for drugs that require a rapid onset of action or if drug elimination is so rapid that an effective concentration in blood cannot be achieved (see below).

Co-administration of certain drugs, antacids, and other products will reduce absorption, either by altering the gastric emptying rate or by binding to a specific drug of interest. Drugs with anticholinergic properties—such as antihistamines, sleeping aids, and antidepressants—will reduce drug absorption. Metoclopramide will modify the absorption of paracetamol (acetaminophen), levodopa, and digoxin. Drug absorption will also be reduced during the interaction of antacids with digoxin, salicylates, and indomethacin, and by the physical binding of digoxin and anticoagulants by cholestyramine. Because of their high use of analgesics, antacids, sleeping aids, digoxin, and antidepressants (13, 14), changes from normal absorption patterns are likely to occur in the elderly.

Current evidence suggests that the morphological structure of the intestinal mucosal surface changes with age. The number of cells comprising the mucosal surface decreases (15), making more probable a reduction in the efficiency of drug absorption. A statistically significant decrease in splanchnic/gastrointestinal blood flow has been demonstrated with increasing age (16); however, for most drugs, this
may not be as clinically important as one might expect. In theory, the diminished blood flow should correspond with a reduced ability to effectively absorb drug presented to the gastrointestinal tract. However, this effect may be offset by the generalized decrease in intestinal motility believed to occur with advanced age, which increases the time available for absorption within the intestinal tract. Furthermore, it is generally thought that the gut is normally well perfused and that the changes in blood flow are not great enough to be a limiting factor in the efficiency of drug absorption.

Despite all of the above age-related physiological changes in gastric emptying, reduced mucosal cell number, reduced intestinal blood flow, and reduced intestinal motility, it is relieving to know that most oral drug absorption is generally not significantly affected by changes associated with aging alone. One exception is the group of drugs that undergo extensive first-pass metabolism in the liver, such as propranolol (17). These drugs may be affected by gastric emptying rate in two ways. First, in the presence of near-normal gastric emptying, the reduced first-pass metabolism resulting from a diminished portal blood flow may provide a greater bioavailability and increased concentrations of these drugs in plasma. However, should disease or other external factors delay gastric emptying, the rate of presentation to the intestine for absorption will be slowed. In this case, elimination of the drug may be rapid enough so that effective blood concentrations cannot be achieved. This will be discussed further in the sections concentrating on drug metabolism and distribution.

Drug Distribution

Once a drug is absorbed from the gastrointestinal tract, it is carried to the site of action via the bloodstream. The majority of drugs exist in an equilibrium between a free (active) and bound form in the blood. The most important binding component in blood is albumin. Because of its importance as a binder of drugs, any significant changes in the concentration of serum albumin will result in changes in the unbound fraction of the drug. Increases in the free (active) concentration of drug should be transient, because the free drug is also available for metabolism as well as distribution into the tissues. Drugs with a high volume of distribution will be rapidly taken up by tissues, resulting in little change in the concentration of free drug. Thus reductions in albumin concentrations will produce an increase in the free fraction of the total drug, but not necessarily in the concentration of free drug.

There is a decline in serum albumin (Figure 1) associated with the normal aging process (18, 19). Concentrations of albumin in serum decline by approximately 15% between ages 30 and 80, with 10% of the elderly having albumin concentrations <30 g/L. Because a lower albumin concentration is often associated with an increase in the free fraction of drug, determinations of total drug concentrations will not always be accurate reflections of free drug concentrations: desired therapeutic concentrations of free drug will be present at lower concentrations of total drug. Clinicians must be aware of this so that they will not make inappropriate adjustments in dosage.

Another protein of potential clinical importance is alpha\textsubscript{1}-acid glycoprotein, an acute-phase reactant that may be increased in illnesses such as inflammatory diseases and infections or after surgery. Several clinically important drugs are appreciably bound by this protein, including quinidine, propranolol (20), lidocaine (21), and tricyclic antidepressants. Unlike albumin, which decreases in concentration in the elderly patient, alpha\textsubscript{1}-acid glycoprotein concentrations will be increased in many cases. These increases in alpha\textsubscript{1}-acid glycoprotein will increase total drug concentrations while decreasing the free fraction of drug.

Changes in protein binding of drugs will be clinically relevant only for the highly bound drugs (>85% bound), and not all of them will be potential sources of problems. Those drugs requiring careful monitoring are those that (a) are normally highly protein bound, (b) have a narrow therapeutic index and margin for safety, (c) have a lower volume of distribution, and (d) are low-extraction drugs that do not undergo significant first-pass metabolism by the liver.

Multi-drug therapy and renal insufficiency are additional factors that will alter drug distribution. As stated earlier, multi-drug therapy is common in the elderly, and is accompanied by an increased incidence of adverse drug reactions. One potential source of toxicity is an increased concentration of free drug resulting from competitive displacement by a second or third drug that has been added to the therapeutic regimen. Renal insufficiency may lead to hypoalbuminemia in the geriatric patient. The consequences of this are similar to those discussed earlier in relation to protein binding. Uremia may result in accumulation of materials that are normally eliminated and that may displace drugs from proteins. There may also be changes in pH, which may affect the degree of protein binding. Renal insufficiency may also reduce the clearance of drug metabolites, which may compete for binding sites on albumin. The importance of renal clearance will be discussed later in greater detail.

Age-related changes in body composition may also alter the normal distribution of a drug within tissue. Total body water and lean body mass decline with age, while the percentage of body fat increases (22, 23). Age-related changes in body composition will be reflected in changes in the apparent volume of distribution (V\textsubscript{d}) for a number of important drugs. Drugs such as lithium, which is distributed largely in the central compartment, and digoxin, which is concentrated within the lean tissues such as muscle, will have a reduced V\textsubscript{d} in the elderly. On the other hand, lipophilic drugs such as diazepam demonstrate an increased V\textsubscript{d} in the elderly (24, 25). The results of studies evaluating V\textsubscript{d} vs age are often conflicting (26–29). Other variables such as renal function, tissue perfusion, general health, and study design may contribute to differences in the observed V\textsubscript{d} values.

Fig. 1. Relationship between age and plasma albumin concentration
From ref. 19, used with permission
Metabolism

The major route of metabolism of drugs is via enzymatic biotransformation and (or) conjugation by the liver. Two major enzymatic pathways are involved in drug metabolism. Phase I reactions, catalyzed by the monooxygenase enzymes of the smooth endoplasmic reticulum, are important in producing more polar and often inactive metabolites, which can be excreted in the urine. Phase II reactions, which can occur in the cytosol, mitochondria, or smooth endoplasmic reticulum, are not catalytic by nature, but involve the production of water-soluble drug conjugates, which can be excreted by the kidney.

During the aging process three potential changes may affect normal drug metabolism by the liver: a decrease in the concentration or activity of the Phase I microsomal enzymes, a decrease in the concentration or activity of the Phase II conjugating enzymes, and a decrease in blood flow to the liver. Data obtained so far indicate that the conjugating capacity (Phase II enzyme systems) of the liver does not change with age. Studies involving the drug isoniazid, which is metabolized through conjugation, have shown that the half-life and clearance rate for this drug are the same in both young and elderly subjects (30, 31). The same bimodal distribution of acetylation rate is observed in all age groups, so it appears that the genetically controlled polymorphic N-acetyl transferase system is preserved in old age (31). Other drugs metabolized primarily by conjugation—e.g., temazepam, acetaminophen, salicylate, and oxazepam—have also been shown to have similar clearance rates in both young and older subjects.

Results of investigations into changes in Phase I microsomal enzyme activity have not been as uniform. Age-related reductions in the metabolism of various drugs, including antipyrine, diazepam, imipramine, amitriptyline, and phenytoin, have been reported (32, 34). Studies involving antipyrine as the drug model have yielded interesting observations and conclusions. This drug has been used to study intrinsic hepatic enzyme activity because antipyrine is not protein bound, is a low-extraction drug, and is metabolized via the microsomal oxidase enzymes of the liver. There is a clear decrease in the metabolic clearance of this drug with increasing age (35, 36). However, studies by Veetal et al. (36, 37) have demonstrated that whereas younger cigarette smokers exhibited a greater clearance of antipyrine than did nonsmokers of the same age (Figure 2), there was no difference between smokers and nonsmokers in the elderly group of subjects. Thus, experimental evidence suggests that it is changes in the degree of enzyme induction related to cigarette usage, rather than increased age, that are the source of the observed decrease in hepatic enzyme activity observed in the elderly. These studies point out the importance of considering habits such as tobacco and caffeine use when instituting long-term therapeutic drug treatment, because age-related decreases in enzyme induction would create a need to decrease dosages as the patient ages.

Liver blood flow has been shown to decrease with age (38) by about 0.5 to 1.5% per year after age 25, in a manner not related to changes in cardiac output (39). This decrease is observed in both smokers and nonsmokers, as well as in both sexes. The consequences of this reduction are most important for high-extraction drugs that undergo significant first-pass metabolism, e.g., lidocaine (40), propranolol, and verapamil (41). These drugs will have both increased bioavailability and increased concentrations in circulating blood, so appropriate reductions in dosage may be necessary.

In summary, the effects of the aging process on drug metabolism have not been clearly delineated, but some general conclusions can be drawn from the available evidence. Drugs with high extraction ratios will exhibit increased concentrations in plasma and longer half-lives in the geriatric patient as a result of diminished hepatic blood flow. Regarding hepatic function and capacity, aging alone may be associated with a decrease in the intrinsic ability of the liver to metabolize drugs via oxidative (Phase I) mechanisms. However, there is strong evidence that extramural factors, especially those with a potential to cause enzyme induction, are of greater significance and account for much of the change observed in drug metabolism during the aging process. These include smoking, dietary habits, drug–drug interactions, and concurrent disease processes.

Renal Excretion

As outlined earlier, the liver is responsible for the bioconversion of active drugs to water-soluble metabolites and conjugates. In addition to the liver, the kidney is also an organ of major importance for the clearance and elimination of drugs, metabolites, and drug conjugates. In fact, renal excretion is very often the primary means of clearance for active drugs. Age-related changes in renal function are among the most important factors that must be considered when one is prescribing drugs for the geriatric patient.

There are several well-documented changes in the kidney that accompany the normal aging process. There is a reduction in renal size and in the number of functional nephrons, possibly as a result of the reduction in renal blood flow (42). Renal blood flow, like hepatic blood flow, is disproportionately reduced relative to any changes in cardiac output. Studies of inulin and iodopyracet clearance (42) have demonstrated that renal function, as reflected in the glomerular filtration rate and tubular secretory capacity, declines steadily after age 20 to 30 years.

Unlike with the liver, changes in the functional capacity of the kidney are much more predictable and can be readily monitored. Creatinine clearance, which can be determined from routine chemical determinations of serum and urine creatinine, is a direct and reliable reflection of the glomerular filtration rate. Creatinine clearance decreases with age (Figure 3) in a manner paralleling the changes in the glomerular filtration rate. Although Rowe et al. (43) constructed a useful nomogram for determining age-adjusted
percentile evaluations of creatinine clearance, the accurate determination of creatinine clearance relies on proper collection of 24-h urine specimens, which may be difficult to control in the elderly population.

Serum creatinine, which is often used to detect changes in normal renal function and integrity, cannot be used alone as a reliable test of renal function in the elderly. As determined in the general population, a large decrease in renal function is often required before a corresponding increase in serum creatinine is observable. This problem is compounded in the elderly population, which already has decreased creatinine production, given the age-related decrease in lean body (muscle) mass, as discussed earlier. Consequently, a reduction in their glomerular filtration is artificially compensated for by the diminished production of creatinine. Despite this potential limitation, various investigators have derived formulas for estimating creatinine clearance from a single determination of serum creatinine, with a correction for age and weight (44):

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\text{Clearance}_{\text{cr}} = \frac{[140 - \text{age (years)}] \times \text{kg body wt.}}{72 \times \text{serum creatinine (mg/dL)}}
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There are no routine tests of tubular secretion. However, evidence suggests that changes in glomerular filtration and tubular secretion proceed simultaneously (45). Davies and Shock (42) have reported that the ratio between the glomerular filtration rate and the tubular secretion capacity remains constant during the aging process, which supports the hypothesis that a nephron loses its function as a unit.

Age-related reductions in glomerular filtration and tubular secretion affect the elimination of many clinically important drugs (46). Glomerular filtration serves as the major route of elimination for digoxin, and there is a direct correlation between digoxin clearance and creatinine clearance (47, 48). The age-related reduction in glomerular filtration is also responsible for the increased half-lives of drugs such as lithium and aminoglycosides in the elderly. Without appropriate reductions in dosage, toxicity is a likely consequence in the older patient. Other drugs and their metabolites are excreted via tubular secretion; these include procainamide, cimetidine, penicillin and cephalosporin antibiotics, salicylates, and diuretics.

Renal insufficiency may result in the accumulation not only of active drugs or their metabolites, but also of inactive conjugates of these drugs. Some evidence indicates that these unexcreted metabolites may ultimately be hydrolyzed back to the active drug form, contributing to undesired effects or drug toxicity (49–51).

Many physiological changes take place during the aging process. Many of these changes have the potential to modify the pharmacokinetics and pharmacodynamics of drugs and must certainly be considered as reasons for altered drug response in the geriatric patient.

In addition to factors discussed here, more needs to be learned about the changes in tissue and receptor response described in the elderly. Also, the elderly are physically less active than the rest of the population, and their dietary habits are often different. The effects of diet, nutritional state, exercise, and body position on drug absorption, distribution, and action all need to be explored further if we are to effectively treat the geriatric population with pharmaceutical agents.

References
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