CHAPTER 7

THERAPEUTIC DRUG MONITORING IN THE GERIATRIC PATIENT

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The complex process of aging is characterized by progressive loss in the functional capacities of organs, a reduction in mechanisms of homeostasis, and altered response to receptor stimulation.[1] These changes combine to increase the susceptibility of elderly individuals to environmental and physical stressors as well as the effects of medications. The prevalence of diseases increases with advancing age, and this increase is accompanied by an increase in the use of medications.[2] Medication therapy is among the most widely used and highly valued interventions for acute and chronic diseases of older adults, yet the use of drug therapy in the geriatric patient is one of the most difficult aspects of patient care.[3,4] The unexpected or exaggerated response to drug therapy exhibited by a geriatric patient compared with a younger patient of the same sex and body weight can frequently be explained through pharmacokinetic or pharmacodynamic changes.[5] Older patients take more medications than younger persons, yet major drug studies are performed primarily on individuals younger than 55 years of age.

The effects of aging on drug metabolism are complex and difficult to predict.[6] These effects depend on the pathway of drug metabolism in the liver, on environmental factors, and on cardiac function.[7] Although many irreversible changes occur with aging, it is now well recognized that individuals age at different rates (chronological and biological age are not necessarily synonymous). Frailty, a biological syndrome in the geriatric patient, is recognized as a confounding factor when considering the impact of aging on drug disposition.[2,8] The frailty of a geriatric patient can alter drug metabolism, and this effect appears to vary from drug to drug. The frail elderly (those that are vulnerable and are at the highest risk for adverse health outcomes) have been shown to have reduced drug metabolism.[9] Frail older adults are identifiable as those at high risk for dependency, institutionalization, falls, injuries, acute illness, hospitalizations, slow recovery from illness, and mortality.[10] Markers for inflammation, such as tumor necrosis factor, interleukin-6, and C-reactive protein, may serve as biochemical markers for frailty and may prove to be a method to characterize an individual's biological age.[11] Because of the frailty of elderly patients, it is important that the first medication prescribed be the most effective choice for the best chance at an optimal clinical outcome.[12] To make the most effective choice, clinicians should take into consideration both personalized pharmacokinetic changes in drug metabolism and pharmacodynamic responses of individual patients, when selecting drug therapies for geriatric patients.

Pharmacokinetic studies comparing young and older adults are often difficult to accomplish due to the problems associated with recruiting healthy older individuals to compare with healthy younger individuals; however, they are increasing in number.[13-29] Problems have been identified with the selection of patient participants and reporting of the clinical trials results to assess age-related pharmacokinetic differences in drugs.[30] Often, participants are the healthy (younger) geriatrics and not the very old (over the age of 85 and/or frail) geriatric patients. The extrapolation of dosages and possible side effects in the very old population may or may not be appropriate.[30] Physiological differences, pathophysiological changes, altered protein binding, and/or concomitant use of medications may account for the altered pharmacokinetics displayed by older patients.[31]

The following examples illustrate the variability of changes that occur in the elderly. There is evidence to show that increased age may delay absorption of transdermal *opioids* but not affect the maximum and steady state concentrations.[32] An infusion of morphine into older patients showed a rapid distribution, followed by a slower elimination when compared to younger patients.[33] Pharmacokinetic studies

have reported no need for dosage changes in the elderly for proton-pump inhibitors, or 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors.[34-36] Data show that the angiotensin converting enzyme inhibitors (ACEIs) *trandolapril* and *moexipril* should be initiated at lower doses in geriatric patients, but no overall dosage modifications are necessary.[37] Other data show that, in the presence of renal impairment, plasma concentrations of ACEIs increase and doses should be adjusted based on renal function.[38] The selective estrogen receptor modulators have variable pharmacokinetic changes associated with aging, with *tamoxifen* and *toremifene* exhibiting increased plasma concentrations with increased age; tamoxifen greater than toremifene; however, neither drug has accompanying package insert recommendations for dosage alterations. No age-related differences in *raloxifene* pharmacokinetics have been identified, but cautionary dosing is advised in both moderate-to-severe renal impairment and in hepatic impairment.[39] Nonsteroidal anti-inflammatory drugs (NSAIDs) exhibit reduced renal clearance in the presence of renal impairment.[40]

Decreased clearance and prolonged half-life of sertraline suggest that steady state concentrations would be higher and achieved later during long-term administration to geriatric patients.[41] A reduced clearance for fosphenytoin, ticlopidine, and ropinirole has been shown in geriatric patients, with the clinical significance of this reduced clearance unknown.[42-44] The fluoroquinolone antibacterials, including ciprofloxacin, and levofloxacin require dosage adjustments based on their predominant renal elimination.[45] The antiepileptic drugs, felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, tiagabine, and topiramate, all exhibit a decrease in apparent oral clearance in elderly patients when compared to non-elderly adult controls.[46] Studies in geriatric patients also show reduced clearance of pregabalin, lacosamide, and retigabine due to less efficient metabolism and/or impaired renal function.[47] Studies measuring the pharmacokinetics of the cholinesterase inhibitors donepezil, rivastigmine, and galantamine in geriatric patients report some changes in pharmacokinetic parameters, but these are not considered clinically significant and no dosage changes are suggested unless patients are in severe renal impairment (galantamine and creatinine clearance <9 mL/min).[48]

Studies reporting data on hypnotic drug disposition and effects in geriatric patients indicate that this population may have reduced metabolic clearance of hypnotic medications, leading to increased plasma concentrations of these agents and/or increased sensitivity to hypnotic medications. Recommended doses of sleep-inducing medications such as triazolam and zolpidem for geriatric patients are generally lower than for non-geriatric patients.[49]

Information regarding dosage alterations based on the pharmacokinetic profiles of drugs in geriatric patients is very important to the clinician as current dosing in geriatric patients is often based on broad generalizations such as "use one-third to one-half the usual dose," or anecdotal data—not on solid pharmacokinetic or pharmacodynamic studies. Pharmacokinetic and/or pharmacodynamic differences in older patients may account for either the toxic or subtherapeutic response that often occurs.

Adverse drug reactions or events (ADEs) and drug-drug interactions (DDIs) occur more frequently in geriatric patients, in part because this population is most likely to be using complex drug therapies.[50-56] The estimated annual rate of ADEs for individuals aged 65 years or older has been measured at more than twice the rate for those younger than 65 years of age.[57] Additional data have shown that for persons 65 years of age and older, the estimated annual rate of ADEs requiring hospitalization was nearly seven times the rate for persons younger than 65 years. Although considerable evidence suggests that an ADE will not occur simply because a patient is elderly, pharmacokinetic and pharmacodynamic changes in the elderly may significantly alter drug disposition and must be considered as contributing to ADEs.[58-60] Symptoms of ADEs can be extremely subtle in an elderly patient and may be manifested by increased frequency of falls, increased confusion, excessive sedation, constipation, urinary retention, decreased oral intake, or a general failure to thrive.[61]

Significant ADEs are most likely observed with drugs having a narrow therapeutic index or saturable hepatic metabolism (e.g., *phenytoin, warfarin,* and *theophylline*) or when elimination is via a single mechanism or pathway. A study of emergency department visits for ADEs showed that drugs that