Antimicrobial Pharmacokinetics and Pharmacodynamics in Older Adults

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KEYWORDS

• Elderly • Antimicrobial therapy • Pharmacokinetics • Pharmacodynamics

KEY POINTS

- Although the adage "start low, go slow" is applicable for most medications in elderly patients, it is inappropriate for most antimicrobials.
- In the elderly, the therapeutic indices of drugs that require serum concentration monitoring (eg, vancomycin, aminoglycosides) may be narrower because of increased sensitivity to adverse effects.
- For time-dependent antibiotics (eg, β-lactams), decreasing the dose and continuing the same dosing interval maximizes efficacy while reducing the risk of toxicity in elderly patients with reduced clearance.
- For concentration-dependent antibiotics (eg, aminoglycosides), using the same dose and increasing the dosing interval maximizes efficacy while reducing the risk of toxicity in elderly patients with reduced clearance.
- Because of their central nervous system side effect profile, clinicians should only select fluoroquinolones for older patients when other options are unavailable due to bacterial resistance, allergy, or other compelling reasons.

INTRODUCTION

Although it is now the eighth decade of the antibiotic era, with the commensurate wealth of data, there are still areas that require greater exploration. The pharmacokinetic (PK), and especially the pharmacodynamic (PD), behavior of systemic antimicrobial agents in elderly patients (>65 years) is a topic that has been inadequately studied.[1,2] Notably, the efforts of a growing number of intrepid investigators are

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gratefully received. There are valid reasons for this. Studies undertaken by manufacturers intended to secure US Food and Drug Administration, European Medicines Evaluation Agency, and other governmental agency approvals frequently exclude elderly patients because of their altered clearance, increased risk for adverse events, and more frequent use of concomitant medications that could interact with the investigational drugs, all of which would confound the results of such research.[3]

Pharmacokinetics is the study of the movement of drugs from the moment of administration through elimination from the body and has been described as "what the body does to the drug." Each of the four phases (absorption, distribution, metabolism, and excretion) has age-related alterations, which are discussed in the next section.

Pharmacodynamics describes the relationship between drug concentration in the body and patient response, or "what the drug does to the body." For most nonantimicrobial drugs PD behavior is directly related to the pharmacologic effect as they interact at the molecular level with host receptors in target (efficacy) and nontarget (toxicity) organs. For antimicrobial agents, however, the target receptors are found in invading pathogens, rather than host organs' receptors. The desired effect of these target receptor-ligand interactions is fatal interference with normal cellular function. Indeed, any interplay of antimicrobial agents with host receptors usually produces only adverse effects, although some antibiotics may have pleiotropic effects, such as modest immunomodulation or other favorable actions.[4–6] Thus, the impact of age on PD results either from alterations in PK, which may affect efficacy and toxicity, or possibly from changes in host receptors responsible only for adverse effects.[7]

Within the elderly population, the frail elderly are especially susceptible to the toxic effects of drugs, including antimicrobials, because of their diminished physiologic reserve. This diminished reserve is attributed to a lower baseline function of one or more organs because of extreme age, a higher incidence of concomitant chronic diseases, and frequent polypharmacy with its attendant increases in adverse effect- and drug interaction-related stressors to physiologic systems.[2,8] Although the adage "start low, go slow" is often applied to drug use in such patients, this is inappropriate for most antimicrobials. Ample evidence shows delayed and inadequate dosing of antimicrobials correlates with increased adverse outcomes, including development of resistance and mortality.[1]

PHARMACOKINETIC CHANGES IN THE ELDERLY

Several PK changes are known to correlate with age.[9–12] For some drugs, however, they are minor changes that do not reach clinical significance or are absent.[13–15] Moreover, there is significant interpatient heterogeneity in the effects of age on PK, resulting in greater variability in these parameters than in younger patient groups. Current data are inadequate to enable identification of which elderly patients will exhibit clinically significant changes and which will not.[2,8] Nevertheless, some general statements can be made.

Absorption

Several alterations in the gastrointestinal tract occur with increasing age and may affect drug absorption. Increased gastric pH, either caused by an age-related reduction in acid production, or the frequent use of acid-reducing medications in older patients, may alter the absorption of low pH-dependent (decreased absorption, seen with ampicillin, ketoconazole, and itraconazole) or acid-labile (increased absorption, seen with penicillin and erythromycin lactobionate) antibiotics. Although acid lability and pH-dependent absorption of antibiotics may be of historical interest, they bear