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

little clinical relevance in the modern era because of innovations in drug delivery, such as enteric coatings and delayed-release formulations, which bypass the low pH environment of the stomach. Older patients often have decreased intestinal surface area and splanchnic blood flow, which may reduce the absorption of most antimicrobials, and decreased gastric emptying and peristaltic activity, which may decrease and/or delay absorption. In general, these changes may slow the rate (lower peak concentration and longer time to peak), but do not significantly decrease the extent (area under the curve [AUC]) of absorption, and are of minor clinical consequence.[1–3,7,8,16] The effects of age on absorption seem to be most pronounced when active transport mechanisms are involved.[16] Several antimicrobials now available have good to excellent oral bioavailability (eg, fluoroquinolones, triazoles, and oxazolidinones), but it is currently unknown whether advanced age correlates with any changes in the absorption of these agents. Age-related changes also affect other routes of absorption, such as dermal, buccal, and conjunctival, but because these routes lack the capacity for systemic delivery of antibiotics, they are not discussed here.

Distribution

The apparent volume of distribution (volume) is a mathematical contrivance that allows the effective concentration of a drug to be derived from its dose. It does not represent actual anatomic or physiologic compartments, and is affected by a variety of factors including plasma protein binding, lipophilicity, tissue binding, and membrane transporters.[2] With age, adipose tissue increases and muscle mass decreases, both of which decrease the elimination of highly lipophilic antimicrobial agents, such as rifampin, fluoroquinolones, macrolides, oxazolidinones, tetracyclines, amphotericin B, and most of the imidazole antifungals. Age-related decreases in total body water contract the volume of hydrophilic drugs (aminoglycosides, β-lactams, and glycopeptides). Hydrophilic drugs that are also weak acids (eg, penicillin, ceftriaxone, and clindamycin) are further affected by the decrease in circulating albumin that also accompanies aging, the net result being increased concentrations of unbound drug.[1,3,7,12,16,17] Plasma α_1-acid glycoprotein, another drug-binding protein, increases with age, which may reduce the free concentration of alkaline antibiotics like the macrolides. Volume is the PK value that determines initial loading doses, and for hydrophilic drugs it correlates closely with body weight. Importantly, for elderly patients with severe infections, treatment with hydrophilic drugs, such as aminoglycosides and glycopeptides, must always be initiated with full loading doses, when such are recommended. Adjustments for renal function are only applied to the ensuing maintenance regimens.[10]

Metabolism

Splanchnic blood flow decreases with age, which also reduces first-pass metabolism and thus increases the serum concentrations of metabolized drugs, such as macrolides, fluoroquinolones (except levofloxacin), clindamycin, tetracyclines, imidazole antifungals (except fluconazole), sulfamethoxazole/trimethoprim, and rifampin.[1,3,12,16,17] Alterations in first-pass metabolism affect only orally administered antimicrobials. Phase I hepatic metabolism (oxidation, reduction, hydrolysis) declines with age, the cytochrome P-450 enzyme systems being the primary pathways. Phase II pathways (methylation, sulfation, acetylation, glucuronidation, and so forth) are largely unaffected by age.[2,7,10,17,18] Some medications are metabolized by phase I pathways, followed by phase II metabolism, but many others are metabolized only by one or the other. Because of the increased number of medications typically prescribed for elderly patients, many of which may interact with antimicrobials via cytochrome P-450

interference or other mechanisms, and the paucity of data in this area, there currently is no clear delineation regarding which of these metabolic changes will predominate in any given patient. Moreover, evidence suggests that the magnitude of interpatient genetic variability overshadows the effects of age on drug metabolism.[16]

Elimination

With age, renal blood flow and glomerular filtration rate decrease, both of which decrease the clearance of renally eliminated drugs.[17,19] Patients greater than 80 years of age have a 40% decline in renal function compared with adults of middle age.[20] Decreased renal clearance of antimicrobials is directly proportional to increases in half-life. Importantly, increased half-life not only necessitates a decrease in daily dose to avoid toxicity, but also prolongs the time necessary to achieve steady-state serum concentrations, which is of particular importance for drugs with narrow therapeutic indices (the ratio of effective to toxic serum concentrations) that require serum concentration monitoring (eg, vancomycin, aminoglycosides). In the elderly, the therapeutic indices of such drugs may be narrower still.[2]

Some published research has challenged the common notion that renal function declines as a function of age per se, independent of other factors.[16,17] The association of aging with decreased renal function is confounded by the high incidence of hypertension, heart disease, and other chronic conditions that also strongly correlate with age. Approximately one-third of elderly patients have a normal glomerular filtration rate.[3,8]

Irrespective of the cause, most elderly patients have decreased renal function and appropriate adjustments must be made for renally cleared antimicrobial agents.[1,3,11,21] Accurate estimates of renal function in older patients are achieved with standard equations,[22] and the equation developed by Cockcroft and Gault[23] is the most commonly used in published guidelines.[2] However, because of the strong correlation of aging with chronic conditions that reduce renal function, this equation may underestimate renal function for the healthiest segment of elderly patients. Age, independent of renal function, has been shown to correlate with several PK changes, which are shown in **Table 1**.

PHARMACODYNAMIC MODELS

With age-related changes in PK as a background, we now review the impact of aging on PD models and discuss what adjustments may be needed when using these models in older patients. For nonantibiotic medications, in addition to altered PK, there may be age-related changes at the receptor level, including differences in receptor density, affinity, or action, which would alter drug PD. In the special case of antimicrobial agents, however, microbial target receptors are "external" to the host and,

Table 1
Drug measures that correlate with age, independent of renal function

Measure	Direction of Change	References
Vd (hydrophilic drugs)	Decreased	24
Cl	Decreased	25–27
Serum concentrations	Increased	28–31
AUC	Increased	32,33
Toxicity	Increased	34

Abbreviations: Cl, clearance; Vd, volume of distribution.

therefore, drug effects at those receptors (once the drug is delivered to the site) are unaffected by patient age.

As with most drugs, delivery of antimicrobial molecules to their site of action depends largely on chemical properties, including lipophilicity, molecular weight, and protein binding, whereas the action of the antimicrobial at the target receptor depends almost entirely on its molecular structure, shape, and charge. In the elderly, fluoroquinolones in particular have a higher incidence of central nervous system toxicities (anxiety, restlessness, insomnia, confusion, hallucinations, psychosis, and seizures), which, in addition to reduced renal function, may be attributable to a more permeable blood-brain barrier, concomitant medications that lower seizure threshold (eg, nonsteroidal anti-inflammatory drugs), or possibly central nervous system receptor changes.[12,20,35,36] For this patient group, clinicians should select fluoroquinolones only when other options are unavailable because of bacterial resistance, drug allergy, or other compelling reasons.

PD models have been developed for antibiotics that take many of these factors into account and accurately describe the relationships between certain PK parameters and the desired clinical outcome (microbial inhibition or eradication). By understanding such models, optimal use of these drugs in the aged is more likely.

Time-Dependent Bacterial Killing

For some antibiotics, bacterial killing best correlates with the amount of time serum concentrations exceed a certain threshold, usually the organism's minimum inhibitory concentration (MIC), a PD model known as time-dependent bacterial killing (T > MIC). Time dependence implies concentration independence. For these drugs, once an optimal concentration is reached, further increasing the concentration does not increase the rate of bacterial killing, possibly because of available binding sites approaching saturation. All of the β-lactam antibiotics (penicillins, cephalosporins, carbapenems, and monobactams) exhibit this behavior.[37] β-Lactams are small molecules that inhibit cell wall synthesis, the target binding sites being located external to the cell membrane. Reducing doses of these drugs to avoid toxicity caused by decreased renal clearance in elderly patients is best done by decreasing the dose and continuing the same dosing interval. This approach optimizes time greater than MIC.[10]

Concentration-Dependent Bacterial Killing

The rate of bacterial killing of antibiotics whose sites of action lie intracellularly (inhibition of protein synthesis via ribosome binding, interference with DNA supercoiling and transcription, and so forth) is usually concentration-dependent, with the strongest correlation being either peak concentration to MIC ratio, or AUC greater than the MIC. Drugs that fit these concentration-dependent PD models include aminoglycosides, macrolides, clindamycin, metronidazole, fluoroquinolones, daptomycin, and tetracyclines.[37] Despite their action on the cell wall similar to the β-lactams, glycopeptides exhibit concentration-dependent bacterial killing with AUC greater than MIC being the strongest correlate. For older patients with decreased renal function being treated with such drugs, reducing dosage regimens is best done by increasing the dosing interval (eg, changing from 6 to 8 hours, 12 to 24 hours) and maintaining the same dose, thus maximizing peak serum concentrations.[10]

MODIFICATIONS IN DRUG DELIVERY BASED ON PHARMACODYNAMIC MODELS

During the past few decades, the body of published medical literature has significantly increased the understanding of how antibiotics work, the PD models that best

describe their actions, and how to maximize efficacy and/or minimize toxicity. We next examine these approaches and the potential age-related changes in each.

Once-Daily Aminoglycoside Therapy

It has been well documented that total daily doses of aminoglycosides given as a single infusion are at least as effective as divided daily doses,[38,39] and this has been validated in elderly patients.[40] This method exploits several PD principles that have been observed with aminoglycosides. The higher dose achieves high serum concentrations, maximizing the peak to MIC ratio. The longer interval between doses is possible because of the postantibiotic effect (continued bacterial killing or inhibition when serum concentrations have declined less than the MIC) seen with drugs of this class. The higher serum concentrations seem to increase bacterial killing without increasing toxic effects. In fact, there is substantial evidence that adverse effects decrease with this method.[39]

The introduction of newer antibiotics with similar spectra and lower toxicities has resulted in the aminoglycosides being seldom used, especially in patients older than 65 years of age who are at higher risk of toxicity. Nevertheless, for an elderly patient with normal renal function, and for whom other options have less favorable risk/benefit ratios, once-daily aminoglycosides may be used with published dosing recommendations.[39] In such cases, the prudent clinician chooses the lower end of the range for loading doses (to correct for reduced total body water), and stops aminoglycoside therapy at the shortest recommended duration once appropriate outcomes are reached.

Prolonged Infusions

In the United States, there was a period when nearly all of the most active antibiotics available (eg, extended-spectrum carbapenems, penicillins, and cephalosporins) were under patent protection, and thus expensive. This prompted investigation into whether the time-dependent bacterial killing of these agents could be used to achieve similar outcomes while reducing total antibiotic use. Prolonging the infusion for normal or reduced doses of carbapenems (imipenem, meropenem, and doripenem), and extended-spectrum penicillins (piperacillin, ticarcillin) and cephalosporins (ceftazidime, cefepime) blunts the peak concentration and prolongs the T > MIC. Continuous infusions of β-lactams have similar effects.[41,42] Clinical outcomes, including mortality, have been found to be superior with extended infusions[42] and it is reasonable to expect no difference in older patients. In the current era of increasing bacterial resistance, prolonged infusions of normal or high doses may increase the activity of these drugs against pathogens with intermediate susceptibility or low-level resistance, although this has yet to be studied.

Lower, More Frequent Doses

Another approach that maximizes the time-dependent nature of bacterial killing with β-lactams is to give smaller doses at more frequent intervals. For example, meropenem, 500 mg every 6 hours, has been compared with 1000 mg given every 8 hours, both by 30-minute infusions. For most susceptible organisms, the T > MIC for these two regimens has been shown to be equivalent.[43,44] As with prolonged infusions, this approach is expected to yield similar efficacy in elderly patients, and potentially decrease adverse events and resistance because of the lower total daily exposure to drug.

SUMMARY

The expectations of antimicrobial agents are starkly dichotomous in that one intends for them to be harmless to host cells, and yet be lethal to the cell (the pathogen) against which they are deployed. (Alas, the search for medications that bind the intended receptor and no other, colloquially the "magic bullet," continues.) This, at least in part, may explain the difficulties faced by those pharmaceutical manufacturers who endeavor to produce novel antimicrobial agents. Nearly all studies that have examined the effects of age on the PK and PD of drugs used cross-sectional study designs that compared young patients with old, rather than the more ideal but also more difficult longitudinal study of patients as they age. That these patients use more medications than any other group, and are a growing segment of the population, heightens the need for more research. Further investigation into the PK and PD of antimicrobial agents in the elderly, with its resultant innovation into better regimen design, will increase the ability of clinicians to use these agents with optimal efficacy and safety in this expanding population.

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