REVIEW

The impact of drug interactions and polypharmacy on antimicrobial therapy in the elderly

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Abstract

Infectious diseases are more prevalent in older people than in younger adults, and represent a major healthcare issue in older populations. Indeed, infections in the elderly are often associated with higher morbidity and mortality, and may present atypically. Additionally, older patients are generally treated with polypharmacy regimens, which increase the likelihood of drug–drug interactions when the prescription of an antimicrobial agent is needed. A progressive impairment in the functional reserve of multiple organs may affect either pharmacokinetics or pharmacodynamics during aging. Changes in body composition occurring with advancing age, reduced liver mass and perfusion, and reduced renal excretion may affect either pharmacokinetics or pharmacodynamics. These issues need to be taken into account when prescribing antimicrobial agents to older complex patients taking multiple drugs. Interventions aimed at improving the appropriateness and safety of antimicrobial prescriptions have been proposed. Educational interventions targeting physicians may improve antimicrobial prescriptions. Antimicrobial stewardship programmes have been found to reduce the length of hospital stay and improve safety in hospitalized patients, and their use in long-term care facilities is worth testing. Computerized prescription and decision support systems, as well as interventions aimed at improving antimicrobial agents dosage in relation to kidney function, may also help to reduce the burden of interactions and inherent costs.

Keywords: Antimicrobial, drug interactions, elderly, pharmacodynamic, pharmacokinetic, polypharmacy
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Introduction

The choice of the class of antimicrobial agents in older patients is often a challenging issue. Indeed, the type of antibiotic should take into account factors related to patient, culprit pathogen (if and when possible), pharmacokinetic and pharmacodynamic properties, as well as the presence of polypharmacy with the inherent risk of adverse drug reactions, or drug–drug or drug–disease interactions.

The aim of this review is to describe the changes in pharmacokinetics and pharmacodynamics occurring during aging, as well as their impact on polypharmacy and drug interactions involving antimicrobial agents. We focus on clinically relevant interactions with non-antimicrobial medications frequently used in older patients. Potentially useful interventions for reducing the risk of drug interactions when prescribing antimicrobials to older patients are also reviewed.

Age-related changes in pharmacokinetics and pharmacodynamics

Aging is generally characterized by changes in all phases of pharmacokinetic processes (Table 1). However, changes in pharmacokinetics may also result from the co-administration of

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TABLE 1. Age-related changes in pharmacokinetics relevant to interactions involving antimicrobial agents

	Age related changes	Potential impact on interactions
Absorption	Increased gastric pH	Increased risk of drug-induced oesophageal lesions
	Delayed gastric emptying	Changes in solubility and chemical stability of drugs
	Reduced splanchnic blood flow	Changes in t_{max} and C_{max}
	Decreased absorption surface	Reduced active transport
	Decreased gastrointestinal motility	
Distribution	Changes in body composition	Increased volume of distribution for lipo-soluble drugs
	Reduced protein-binding sites	Reduced volume of distribution for water-soluble drugs
	Changes in blood–brain barrier permeability (conflicting evidence)	Increased toxicity from selected drugs in the presence of severe hypoalbuminaemia
		Increased bioavailability of drugs displaced from protein-binding sites
Metabolism	Reduced hepatic blood flow and overall liver mass	Inhibition and/or induction of cytochrome P450s in the context of polypharmacy regimens
	Less effective first-pass metabolism and phase I metabolism	
	Reduced cytochrome P450 activity (conflicting evidence)	
Excretion	Reduced kidney glomerular filtration rate and tubular secretion	Impaired elimination of water-soluble drugs

selected drugs, as is the case for several antimicrobial agents, leading to clinically relevant interactions.

Absorption

Reduced oesophageal peristalsis and gastric acid secretion [1] usually have only a minor impact on oral antibiotic absorption. However, an excess increase in gastric pH, as can be produced by long-term use of proton pump inhibitors, can alter solubility and chemical stability of β-lactams, macrolides and azoles, reducing their bioavailability [2]. Age-related reduced gastric emptying and peristalsis [3,4], splanchnic blood flow and bowel surface area [5] can reduce the bioavailability of amoxicillin and clavulanic acid when assumed following the meal [6]. Reduced active transport function may also lead to clinically important drug interactions, which are of particular importance in older patients treated with complex polypharmacy regimens [7,8]. Macrolides may increase serum concentrations of calcium channel blockers and sulphonylureas by inhibiting intestinal cytochrome P450 3A4 (CYP3A4), and cause digoxin toxicity by inhibiting intestinal P-gp [9]. The inhibition of intestinal CYP3A4 by macrolides may increase the risk of toxicity from several drugs, including midazolam, cyclosporine, statins, antiarrhythmics, tricyclic antidepressants, antipsychotics and warfarin. Finally, specific antifungal agents, such as itraconazole and caspofungin, can also inhibit CYP3A4 and P-gp [9].

Distribution

Overall, the volume of distribution for lipophilic drugs may increase with a prolonged half-life [10], whereas water-soluble drugs may have a smaller volume of distribution causing a more rapid increase in plasma concentrations [11], and indicating the need for lower initial doses [12]. Age-related changes in plasma protein binding seem to be less important for drug therapy, as steady-state unbound drug concentration often redistributes and remains unaltered [9,13]. More pronounced changes in protein-binding capacity are generally due to disease-related hypoalbuminaemia [14]. A recent retrospective observational study of 94 older patients with methicillin-resistant *Staphylococcus aureus* hospital-acquired pneumonia showed that patients with severe hypoalbuminaemia had significantly longer vancomycin half-life (33.2 + 5.4 versus 24.9 + 1.6; p 0.049), greater risk of 28-day mortality in relation to high values of the area under the concentration curve (AUC)/minimum inhibitory concentration (MIC) (250–450 or >450 μg × h/mL), and more frequent nephrotoxicity (26% versus 8%, p <0.001) compared with patients with mild hypoalbuminaemia [15]. Hence, severe hypoalbuminaemia needs to be addressed when vancomycin is prescribed to older patients.

Protein-binding drug interactions involving antimicrobial agents also deserve mentioning: co-trimoxazole is known to increase serum concentrations of methotrexate and sulphonylureas by displacing them from plasma protein-binding sites, resulting in a clinically relevant increased risk of hypoglycaemia and severe bone marrow depression [9], respectively.

Metabolism

The bioavailability of drugs undergoing extensive first-pass metabolism increases [16,17], while the bioavailability of drugs that need to be activated in the liver is reduced [18]. In elderly patients, the hepatic clearance of drugs undergoing flow-limited metabolism may be reduced up to 40% [19,20]. Hepatic clearance by cytochrome P450 (CYP) -mediated phase I oxidization, reduction and hydrolysis reactions is impaired to a greater extent with respect to clearance mediated by phase II conjugation reactions, mainly because of the reduced hepatic blood flow and overall liver size [19,20]. The effects of aging on the CYP activities are still a matter of debate [21–23]. An age-related 20% reduction in the metabolism of CYP2D6 substrates has been observed [24,25]. Such a finding has not been confirmed for the CYP3A subfamily, which is responsible for the elimination of more than 50% of its substrates [26–28]. Additionally, the activation of some important CYPs, including CYP3A4, CYP2D6 and CYP1A2, does not seem to change with aging [29,30].

