Introduction

Aging is not a disease but results in a progressive shift in homeostasis characterized by alterations in metabolic activity and an increase in age-related problems. The normal physiology of aging results in an intrinsic decrease in the functional reserve of the major organ systems (liver, kidney, and cardiovascular), redistribution of regional blood flow, and changes in body composition including a decrease in lean body mass (total body water and cell mass) and an increase in fatty tissue. Additional intrinsic changes in physiology associated with aging that influence drug disposition in geriatric patients include decreased drug absorption from the gastrointestinal tract, decreased hepatic metabolism, and decreased renal excretion. In addition, systemic diseases involving the gastrointestinal tract, liver, kidney, and cardiovascular system are more common in geriatric patients further impacting drug disposition.

Aging and disease can have a significant influence on drug pharmacokinetics (drug absorption, distribution, metabolism, excretion) and pharmacodynamics (drug action and response of patient) potentially resulting in clinically significant adverse drug reactions in geriatric patients. For example, as cardiac output declines the major organs preferentially perfused including brain, heart, and kidneys. The altered distribution of blood and body composition in geriatric patients impacts the distribution of drugs and potentially increases their risk of toxicity.

The changes in the body composition and the major organ systems associated with aging or disease can significantly impact the clinical use and clinical pharmacological response of drugs. Outlined below are some of the more common alterations associated with drug therapy in geriatric patients or patients with major organ dysfunction. The complexity of drug interactions in the geriatric patient is multifactorial and additional factors to consider in treating geriatric patients include nutritional status, drug-drug interactions, and co-morbidities.

Body composition

Physiological changes with age that influence the distribution of drugs in the body include a decrease in lean body mass and total body water. Together this results in a decrease in the volume of distribution available to water soluble (or hydrophilic) drugs (ex. digoxin, aminoglycosides, atenolol). For example digoxin, should be dosed on lean body weight to avoid excessive plasma concentrations. In contrast the increase in body fat favors the deposition of fat soluble (or lipophilic) drugs (ex. benzodiazepines, lidocaine, steroid hormones).

In addition, the concentration of circulating albumin decreases with age with the potential of impacting the fraction of pharmacologically active free drug available. Acidic drugs that are highly protein bound (ex. aspirin, NSAIDs, benzodiazepines) are most likely to be impacted by decreasing serum albumin levels resulting in greater pharmacological activity.

A drug’s pharmacodynamics is a function of the concentration of free drug at the site of action and the affinity of the drug for its target receptor. Altered drug-receptor interactions (ex. altered receptor binding affinity, density, and/or regulation) in geriatric patients can result in increased drug sensitivities relative to younger individuals. The two groups of commonly used drugs with altered pharmacodynamics in geriatric patients include the benzodiazepines and non-
steroidal anti-inflammatory drugs (NSAIDs). Altered pharmacodynamics results in oversedation in geriatric patients in association with benzodiazepines administration. In geriatric human patients altered reaction times and increase-dose response are associated with the use of benzodiazepines. Elderly humans chronically taking NSAIDs are over twice as likely to develop peptic ulcers compared to elderly patients not receiving NSAIDs. In addition, geriatric patients are at increased risk for other NSAID adverse reactions including acute renal injury and hepatotoxicity.

**Gastrointestinal tract**

Physiological changes in the gastrointestinal tract with age and/or disease include reduced gastric acid production and emptying, decreased intestinal motility, reduced intestinal perfusion, and a decrease in mucosal surface area. In addition as cardiac output decreases with age the gastrointestinal blood flow diminishes. Collectively these changes in gastrointestinal tract physiology can result in changes in the rate and extent of absorption of orally administered drugs. While the anticipated clinical effect of these gastrointestinal changes is difficult to predict and in most cases is likely not clinically relevant; the rate of oral drug absorption maybe prolonged, delaying the drug’s onset of action.

**Cardiovascular system**

Aging and disease of the cardiovascular system alters the distribution of blood flow to tissues. The redistribution of blood flow results secondary to changes in water and sodium balance and chronic sympathetic nervous system activation. Organ systems most significantly impacted by changes in blood flow that also impact the absorption, distribution, metabolism, and elimination of drugs include the kidneys, gastrointestinal tract, and liver.

Examples of alterations in drug disposition associated with heart failure include the decreased rate and amount of oral furosemide absorbed in patients with congestive heart failure and elderly patients. The risk of digoxin toxicity (arrhythmias due to cardiotoxicity or nausea associated with CNS toxicity) is increased in patients with congestive heart failure and geriatric patients. For example, low potassium concentrations (secondary to furosemide administration) can increase the risk of digoxin toxicity and decrease the efficacy of the antiarrhythmic lidocaine. In addition, patients with heart disease or history of heart failure are on multiple drugs that modulate the sympathetic nervous system, control heart rate and rhythm, and impact the electrolyte and fluid balance of the body. Multidrug therapy increases the risk of adverse drug effects or drug interactions.

**Kidneys**

The kidney is the major organ for drug elimination and has a significant role in maintaining the body’s fluid and electrolyte balance. Kidney function is significantly impacted by aging not only in association with a loss in mass but also altered perfusion. Altered blood flow in the kidney, associated with aging and/or disease, results in a decrease in glomerular filtration rate and the secretory function of the nephron. In addition, increased fluid retention associated with kidney disease can alter the volume of distribution of drugs, especially drugs primarily distributed in plasma (penicillins, cephalosporins, and aminoglycosides).

Reduction in kidney function has the most significant clinical impact on drug disposition, as renal clearance is impacted by changes in glomerular filtration, active-tubular secretion, and passive tubular reabsorption. Drugs of particular concern are drugs or drug metabolites with a high kidney excretion including penicillins, aminoglycosides, digoxin, ACE-inhibitors, and benzodiazepines. A loss in the ability of the body to eliminate drugs through the kidney results in increased drug plasma concentrations, increased elimination half-lives, and an increased risk for adverse drug reactions or
toxicity, even when standard dosage regimens are administered. Drugs excreted primarily by the kidneys often require drug dosage adjustment to minimize the risk of toxicity in geriatric patients or patients with kidney dysfunction.

Examples of potential drug interactions in patients with kidney disease are associated with the use of antacids and phosphate binders. Antacids and phosphate binders are commonly used in patients with kidney disease but they also reduce the absorption of orally administered antibiotics including fluoroquinolones, tetracyclines, and sulfonamides.

Liver

The liver is the primary site of drug metabolism and with age the liver undergoes anatomic and functional changes. Hepatocyte number and function decrease, hepatic and splenchnic blood flow decrease, and the intrinsic activity of drug metabolizing enzymes are reduced.\(^2\) In addition, hepatic blood flow decreases with a decrease in cardiac output which may influence the clearance of drugs by the liver.

Although overall liver function is maintained with age; aging results in a decrease in phase I metabolism (oxidation, reduction, hydrolysis) of some drugs (ex. diazepam) and hepatic metabolism is often decreased for drugs whose hepatic metabolism is blood flow limited (ex. lidocaine, beta-blockers). Factors that impact hepatic clearance of drugs include intrinsic enzyme activity, biliary excretion, hepatic blood flow, and protein binding. Key drug metabolizing enzymes (phase I and phase II) are needed to convert lipophilic drugs to more water soluble metabolites for excretion by the kidney. With a progressive loss of liver function comes the risk for adverse clinical events, although for most drugs unless fulminate liver failure is present it is difficult to accurately predict the need for dosage adjustments associated with liver disease.

In association with the loss of liver function is the loss of synthetic function including the development of hypoalbuminemia. The main pharmacokinetic influence of hypoalbuminemia is on drug distribution with the clinical impact being most significant for acidic, highly protein bound drugs (aspirin, NSAIDs, benzodiazepine). The loss in circulating albumin levels results in a decrease in available binding sites for drugs in plasma. As less drug is bound to albumin the concentration of free drug in circulation significantly increases and it is the free drug fraction that is pharmacologically active and available to interact with target receptors, distribute to tissues, or available for metabolism.

References