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Pharmacokinetic Modifications and Drug-Drug Interactions in Clinical Monitoring of the Elderly: A Short Review

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Abstract

The combination of drugs may be a result of a necessary therapeutic strategy against a single disease or a fortuitous treatment of two or more health disorders. In either case, a consequence of such approach is the increased risk of drug interactions and subsequent adverse effects. For the elderly, the probability of these events is significantly increased compared to other age groups, not only because of combining medications but also age-related pharmacokinetic (absorption, distribution, biotransformation and excretion processes) alteration. Since the growth rate of the elderly population worldwide is rapidly increasing, clinicians should be extremely cautious of the drugs prescribed to older patients in order to minimize drug interactions and therapeutic failure.

Keywords: Aging; Pharmacology; Polypharmacy; Adverse drug reactions; Geriatrics

Introduction

Combination drug therapy is a common practice in clinical medicine. They are often used as an approach to enhance the desired pharmacological effect (*e.g.*, paracetamol and codeine), prevention of resistance (*e.g.*, β-lactam antibiotics and β-lactamase inhibitors), or yet the prevention of adverse side effects (interactions of physiological or pharmacological antagonism). All of these approaches intend to ensure greater efficacy of and patient adherence to the pharmacological treatment, since they aim to maximize drug effects and reduce the possible undesirable effects generated due to their use.

Despite seemingly adequate, and many times necessary, the employment of more than one drug to treat a given disease should be conducted judiciously and carefully because of the risk of dangerous drug interactions. However, combination chemotherapy, also known as polypharmacy, and particularly the adverse effects caused by them, is a very poorly explored and even neglected factor in clinical practice [1,2]. Epidemiological studies indicate that adverse drug reactions (ADRs) produced by drug interactions affect progressively from hospitalized patients to outpatients, where there is usually lack of monitoring and professional care. Hypothetically, the estimation of probabilities of potential interactions through combinatorial analysis reveals, for example, that co-administration of 3, 5 or 7 drugs provides interaction chances of 15, 50 or 100%, respectively [3]. Furthermore, over 80% of registered ADRs are characterized as type A, *i.e.*, arising from an exaggerated, dose-dependent drug effect and, by definition, are predictable and preventable, in contrast to the low prevalence of type B ADRs, *i.e.*, unexpected reactions and disconnected from the action of the drug (idiosyncratic) [4]. The major drug classes responsible for type A are antibiotics, anticoagulants, positive inotropic agents, diuretics, antidiabetic agents, non-steroidal anti-inflammatory drugs (NSAIDs), opioids and antineoplastics [4].

In the elderly population, the development of ADRs related to drug interactions is even more complicated because the existence of chronic diseases, polypharmacy, inadequate identification by and information to the patient of the effects of the prescribed drugs, noncompliance to the therapeutic regimen, self-medication, nutritional problems, reduction of financial resources and physiological changes related to aging (Table 1) increase the risk of the manifestation of unwanted interactions [5]. In fact, the latter seems to be a major challenge for the rational prescription of drugs in this population group [6,7]. According to the fertility rates and longevity worldwide, the percentage of elderly is increasing faster than the rest of the population. In developing countries like Brazil, for instance, the estimate for 2020 is 30 million people above 60 years of age (about 13% of the population), while in European countries and in the United States the current fraction of this group is over 15% [8]. Thus, in developed countries the overall occurrence of ADRs in geriatric hospitals may reach 20% and its nature follows the same pattern described above (mainly type A) [4]. Interestingly, the drug classes that often cause more type A ADRs are also those administered with greater frequency to geriatric patients in Brazil [9] and abroad [10].

Chronological age itself seems to have interference on the fate of drugs in the body; however, factors such as gender, ethnicity and the genotype of the patient generally have more importance [11]. Nevertheless, the organic changes that occur in the elderly could promote significant changes in pharmacokinetic and pharmacodynamic profiles

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and therefore unexpected interactions. Thus, the possible effects of physiological changes caused by aging on the pharmacological processes and resulting interactions, comparing the risks and benefits of drug therapy in geriatric patients, are described.

Pharmacokinetic changes in geriatric patients

Absorption: Absorption involves the passage of drug molecules through the barrier(s) available between the administration site and the vascular compartment. Such process is crucial to the drugs that are administered via enteral or parenteral routes can reach their target and generate the desired pharmacological response.

For drugs administered orally, both the C_{max} (maximum plasma concentration achieved by a drug), T_{max} (time in which this is achieved) and AUC (area under the curve, giving the extent to which this process occurs) are directly influenced by the biochemical and physiological processes that govern the functioning of the gastrointestinal tract. The pH of the digestive tract, the rate of gastric emptying, intestinal smooth muscle tone, integrity of the intestinal surface (Kerckring folds, duodenal villi and microvilli), can significantly interfere with the absorption of drugs administered by this route. Any modification in these factors caused by different physiological, pathological or pharmacological conditions could cause failure of drug therapy.

As the elderly can present several slightly altered gastrointestinal properties (Table 1) and is more prone to chronic diseases, which often leads to the use of various types of medications concomitantly, special attention should be given to this group. Nevertheless, age usually does not affect the absorption of drugs that permeate the intestinal epithelium by passive diffusion in a clinically significant manner, with a few exceptions as indomethacin, prazosin, digoxin, and ciprofloxacin. Moreover, some ions (*e.g.*, calcium, iron), vitamins, and maybe some nucleoside derivatives and gabapentin, which utilize the active transport or facilitated diffusion to cross this epithelium, can be absorbed at a slower rate [12]. In general, however, the enteral absorption is not a critical factor in the onset of interactions [13].

Changes in pH of the gastrointestinal tract may also affect the dissolution of oral preparations. For example, the elevation of gastric pH may promote the early dissolution of formulations in the stomach with enteric coating (gastro-resistant) and affect the integrity of the drug and its absorption, which may be augmented in the case of basic drugs. A pharmaceutical product designed to dissolve in the normal gastric pH may also not dissolve properly in a higher pH, which can lead to incomplete absorption of the drug [3,14]. O'Connor-Semmes et al. [15] showed that in the presence of ranitidine, the AUC of triazolam was 10% higher in adults < 60 years old and 30% higher in those who were older than that. By evaluating the kinetics of the metabolite α-hydroxy-triazolam, they discarded the possibility of interaction through biotransformation and excretion of triazolam, suggesting that the higher gastric pH achieved by the elderly with ranitidine probably facilitated the absorption of triazolam, a benzodiazepine sensitive to acid pH. On the other hand, a more recent study with ketoconazole, whose ability of dissolution is inversely proportional to pH, revealed by telemetry that, in fact, the rate of hypochlorhydria in the elderly is low (around 5%) and similar to young adults, questioning whether this factor is as common as it is believed in that population [16].

System	Observed alteration
General	↓ body weight ↓ basal metabolic rate ↓ body water ↓ percentage of lean body mass ↑ percentage of fat body mass
Circulatory	↓ cardíac output ↓ tissue blood flow ↓ plasma albumin
Gastrointestinal	↓ gastric acid production ↓ gastric emptying rate ↓ intestinal motility ↓ blood flow ↓ absorptive surface
Hepatic	↓ mass ↓ blood flow (arterial and/ou portal)
Renal	glomerular filtration rate ↓ tubular function
Pulmonary	↓ vital capacity

(↑) Increase; (↓) Decrease

Table 1: Physiological alterations in the elderly with potential to influence drug pharmacokinetics (modified from Klotz [6]).

The decrease in gastric and intestinal motility present in the elderly, similar to the elevation of gastric pH, may be a factor that exacerbates interactions [17]. In theory, opioid and cholinergic antagonists, which tend to decrease gastric emptying and gastrointestinal transit, could more significantly restrict the absorption of other drugs in older subjects due to an already compromised basal motility [3,14]. Conversely, some reports show that the gastric emptying time at advanced age is not different from young adults [16].

Despite the reduction of blood perfusion clearly have no influence on the enteral absorption, this factor can lead to a significant reduction in the rate of absorption of drugs administered by the most commonly used parenteral routes. Indeed, the intramuscular administration is generally avoided in the elderly by the possibility of erratic absorption – *e.g.*, antibiotics [14] – and the risk of formation of sterile abscess [12]. For inhaled drugs, especially anesthetics, an important parameters that declines with age is the minimum alveolar concentration, generally explained by alterations of the autonomous nervous system [18].

Distribution

After the drug reaches the systemic circulation, it undergoes a phenomenon called distribution. This stage is characterized by the rapid spread of the drug into various body compartments, a process dependent on physicochemical characteristics of the drug, its solubility in water or lipids and its affinity to plasma and tissue proteins.

The apparent volume of distribution (V_d) is the pharmacokinetic parameter used to estimate the distribution profile of a drug in the body and relates the total amount of drug administered to their plasma concentration. Thus, the greater the affinity of the drug to plasma or tissue components, the lower or higher will be its V_d, respectively.

In the elderly there is a significant change in body water:fat balance. The lean body mass, especially muscle and bone mass, declines with age as well as the total body water content (up to 15%) [12]. In contrast, total body fat in older subjects reaches 35% in men and 45% in women, compared to 20% and 35% of the respective genders in the young [11, 12]. This may lead to considerable changes in distribution patterns of hydrophilic and lipophilic drugs in this group of individuals [14], *i.e.*, in the former case (*e.g.*, aspirin, non-depolarizing neuromuscular blockers, H_2 antagonists, lithium), V_d may be reduced in the elderly and the concentration in plasma is elevated when administered at the same dose used in young adults [11,12]. In the latter case (*e.g.*, benzodiazepines, tricyclic antidepressants, lidocaine, verapamil), the increase of V_d can rise the elimination half-life (t½) of the drug, since

this parameter is closely associated, and in direct proportion, to the V_d [11,12]. Interestingly, the concomitant use of diuretics can reduce even more the extracellular fluid content, increasing the risk of toxicity [13]. Furthermore, the frail elderly with decreased weight has a decline in the percentage of body fat and increased V_d even for lipid-soluble substances [13].

Plasma proteins, acceptors of most drugs used clinically, may display variations of concentration throughout aging. While serum albumin may be reduced by up to 20%, α_1-acid glycoprotein may increase [11-14]. However, these changes have no clinical relevance in general, as evidenced by Grandison and Boudinot in their excellent review [19], except when other conditions trigger/exacerbate such variations such as malnutrition and disease (*e.g.*, cancer) and when the drug has a high rate of binding to these proteins (Box 1) and/or has a low therapeutic index [11,13]. Certain anionic (acidic) drugs as valproate, naproxen, diazepam, ceftriaxone and enalaprilat (the active metabolite of the prodrug enalapril), which preferentially bind to albumin, and cationic (basic) drugs such as lidocaine, propranolol and chlorpromazine, which bind to the α_1-acid glycoprotein, have their free fractions in plasma modified by age [19,20]. As the practice of polypharmacy is common to these patients, the presence of other drugs that may compete for binding to the same plasma protein in high-affinity sites may also be relevant. Well-known examples of this type of interaction in the case of albumin are warfarin, phenylbutazone, sulfonamides, phenytoin and valproate, and benzodiazepines, probenecid, semi-synthetic penicillins and intermediate-chain fatty acids [19,20].

Biotransformation

In the elderly, changes in the bioavailability of drugs promoted by changes in drug biotransformation, a step in the process of elimination pharmacokinetics, are relatively frequent. On average, the elderly presents 70% of the total capacity of biotransformation compared to young adults [11]. Chronic diseases, malnutrition, changes in liver physiology, and the use of multiple medications are the main factors that increase the potential of drug interactions in patients of this age group and undermine the therapeutic efficacy.

Physiologically, there is a reduction of liver blood flow and volume (about 30-40%) [12,21] although the quantitative changes of liver function and histology are minimal [22,23]. The discrepancy of the findings of reduced biotransformation, especially oxygen-dependent, in the elderly, led to proposal that aging is associated to pseudocapillarization of liver sinusoidal endothelium but without alteration of enzymatic content or activity [24-26]. These factors undermine the hepatic blood flow and, consequently, the efficient oxygenation of and arrival of nutrients to hepatocytes, the metabolism of these cells and, especially, the access of the drug to the liver to be biotransformed [25].

Low (0-25%)	Intermediate (25-75%)	High (>75%)
ampicillin	chloramphenicol	acetylsalicylic acid
antipyrine	digoxin	amphotericin B
cephalosporins	lincomycin	ethacrynic acid
cycloserine	nitrofurantoin	clofibrate
ethanol	penicillins	digitoxin
kanamycin	pentobarbital	estrogens
lithium	quinine	glucocorticoids
paracetamol	secobarbital	griseofulvin
phenobarbital	tetracyclines	oral anticoagulants
strophantidin	thiopental	indomethacin
xanthines	trimethoprim	insulin
		mefenamic acid
		nalidixic acid
		phenylbutazone
		phenytoin

Box 1: Binding capacity of drugs to plasma proteins.

The nutritional condition of the patient also has an important influence on the rate of biotransformation. Malnutrition, characterized by protein deficiency, impairs the synthesis of enzymes directly, causing a significant impairment of metabolic and biotransforming capacity of tissues. Geriatric patients under the ideal weight have a lower extent of drug biotransformation than those of normal weight [27,28].

Besides the physiological changes and malnutrition, some chronic diseases that frequently affect patients in this age group may also cause relative hypoxia and other pathophysiological features typical of such disorders, *i.e.*, enzymatic and hormonal alterations (hepatitis); lipid macrovesicles in hepatocytes, inflammation and Mallory corpuscles lesions (steatosis); vascular (due to diabetes mellitus) and systemic circulation disorder (cardiopathies).

Nonetheless, among the identified interactions including those discussed above, the drug-drug interactions are probably the most important in older people, especially those that alter the biotransformation process.

The biotransformation of xenobiotics occurs in enterocytes and/or hepatocytes in two phases: Phase I and/or phase II. Phase I (functionalization or non-synthetic phase) appears to be most influenced by age and is promoted by microsomal enzymes, among which stands out the mixed function oxidase system, known as cytochrome P_{450} (CYP), playing an oxidative function over lipophilic substrates [19]. CYP is a hemoprotein that presents several isoforms which differ in the inducibility and inhibitory pattern by certain substances, and probably also in the specificity of its catalytic action [19]. Among the CYP isoenzymes, the most commonly involved in drug biotransformation are CYP3A4, CYP2D6 (as a whole, these two are responsible for biotransformation of approximately 75% of all drugs), CYP1A2, CYP2C9, CYP2C19 and CYP2E1 [3]. Importantly, the activity and expression of the major isoform, CYP3A4, is dependent on normal liver function and is progressively decreased after its optimal performance in adulthood, reflecting the relative inability of biotransformation of older patients [3,11,21]. On the other hand, CYP2D6, which is responsible for ~25% of drug biotransformation, is particularly resistant to the relative hepatic impairment seen in the elderly [3,11,29]. Clinical problems of toxicity and ADRs can be minimized or avoided when knowing the CYP involved in the biotransformation of a given drug. In geriatric patients, several reports have shown that some drugs are poorly metabolized while others are not, although sometimes drugs from both metabolizing groups are targets of the same CYP (Table 2), indicating the complexity of the whole process [3]. In any case, it is important to bear in mind that elderly patients have a high incidence of CYP-metabolized drug treatment, which may increment the possibility of drug interactions and ADRs [30].

Although CYP activity and the resultant biotransformation ability depend on genetic polymorphism [29], this set of enzymes can undergo induction or inhibition, where the effect of a drug can influence the biotransformation of others. This leads to changes in the time of onset

and duration of effect, pharmacokinetic tolerance, therapeutic failure and/or worsening of toxicity.

The enzymatic inhibition is responsible for most drug interactions [31], and occurs by different mechanisms, but especially by the competition of two drugs for the same enzyme. The degree of inhibition depends on the permanence of the inhibitor drug in the body as well as its affinity to the biotransforming enzyme and dose administered [3]. Such inhibition of microsomal enzymes decreases the rate of hepatic and/or intestinal drug biotransformation as well as the total clearance, increases the serum concentrations of the free and total drug, the t½ of the drug in serum and clinical effects if the metabolites are inactive, and slows the production of metabolites. The main drugs involved in reversible enzyme inhibition are ketoconazole (non-competitive), erythromycin, nifedipine, omeprazole, progesterone, quinidine (competitive), fluconazole and fluoxetine (mixed) [19]. Other examples are shown in Table 4.

The process of enzyme induction, as it involves the synthesis of new enzymes via CYP gene transcription promoted by inducing drugs, usually takes longer and the degree of induction depends on the same variables described above for the enzyme inhibition [3].

Thus far, however, no conclusive comparative data on the presence or absence of differences between the extent of enzyme inhibition or induction in the elderly and young adults was obtained [13].

Many drugs are also biotransformed by phase II (conjugation or synthetic phase) involving reactions that produce conjugates such as acetylation, glucuronidation and sulfation, but these reactions are rarely affected by age [21,32]. Moreover, the amount of studies on the subject is much smaller than the reactions of phase I. Some examples can be seen in Table 3.

Pharmacological class	Drug*	Impaired metabolism	CYP
Antihypertensives	nifedipine, felodipine, diltiazem propranolol irbesartan verapamil	yes no no yes	3A4/3A5 2D6 2C9 several
Antiarrhythmics	amiodarone, lidocaine	yes	3A4/3A5
Anxiolytics/hypnotics	triazolam, zolpidem diazepam midazolam	yes no no	3A4/3A5 3A4/3A5 3A4
Antidepressants	amitriptyline sertraline fluoxetine, nortriptyline, venlafaxine citalopram imipramine	yes no no no yes	3A4/3A5 3A4/3A5 2D6 2C9 2C19
Anticonvulsants	carbamazepine phenytoin	yes no	3A4/3A5 2C9
Antipsychotics	risperidone	no	2D6
Analgesics (opioids)	fentanyl alfentanil	yes no	3A4/3A5 3A4/3A5
NSAIDs	paracetamol naproxen celecoxib, diclofenac ibuprofen	no yes no no	3A4/3A5 2C9 2C9 several
Antibiotics	cyclosporine	yes	3A4/3A5
Anticoagulants	warfarin	yes	2C9

* When the drug belongs to two or more pharmacological classes, it is presented in only one class
CYP – cytochrome P_{450}; NSAIDs – Non-steroidal anti-inflammatory drugs

Table 2: Phase I drug biotransformation characteristics in the elderly (modified from Turnheim [12]).

Drug A	*Interaction with drug B*	*Effect on A (mechanism)*
Carbamazepine	enzymatic inhibitors, verapamil	↑ (↓ *biotransformation of A*)
Cyclosporine	enzymatic inhibitors	↑ (↓ *biotransformation of A*)
	enzymatic inducers	↓ (↑ *biotransformation of A*)
Digoxin	amiodarone, diltiazem, verapamil, ACEi, NSAIDs	↑ (↓ *excretion of A*)
	atorvastatin	↑ (*unknown*)
	antiacids (with Mg^{2+} or Al^{3+}), cholestyramine, colestipol	↓ (↓ *absorption of A*)
Lithium	NSAIDs, diuretic tiazídicos	↑ (↓ *excretion of A*)
Quinolones	cholestyramine, colestipol	↓ (↓ *absorption of A*)
	enzymatic inhibitors, quinolones	↑ (↓ *biotransformation of A*)
Theophylline	enzymatic inducers	↓ (↑ *biotransformation of A*)
Thyroxine	enzymatic inducers	↓ (↑ *biotransformation of A*)
TCA	enzymatic inhibitors[a]	↑ (↓ *biotransformation of A*)
Warfarin	enzymatic inducers[b]	↓ (↑ *biotransformation of A*)
	cholestyramine, colestipol	↓ (↓ *absorption and* ↑ *excretion of A*)
	enzymatic inhibitors	↓ (↑ *biotransformation of A*)
	enzymatic inducers	↓ (↑ *biotransformation of A*)
	clofibrate, danazol, gemfibrozil, NSAIDs, phenytoin, stanozolol, tamoxifen, thyroxine	↑ (*pharmacodynamic and/or pharmacokinetic potentialization*)

[a]Examples of well-known inhibitors: amiodarone, fluconazole, miconazole, ketoconazole, erythromycin, clarithromycin, sulfonamides, omeprazole, cimetidine and ciprofloxacin.
[b]Exemples of well-known inducers: rifampin, phenobarbital, phenytoin, primidone and carbamazepine.
(↑) Increase; (↓) Decrease
ACEi – angiotensin converting enzyme inhibitors; NSAIDs - Non-steroidal anti-inflammatory drugs; TCA – Tricyclic antidepressants

Table 3: Pharmacological interactions of clinical importance in the elderly.

Excretion

Renal excretion of drugs is a phenomenon basically dependent on three processes: glomerular filtration, active tubular secretion and passive diffusion across the tubular epithelium. In glomerular filtration, molecules with molecular mass less than 20 kDa can reach up to the filtrate (glomerular ultrafiltrate) by passive diffusion through the fenestrae of glomerular capillaries. Thus, the free fraction of the vast majority of drugs are able to freely cross this barrier, but the fraction associated to plasma proteins such as albumin is impeded to undergo this process and may be subject to drug interactions – resulting both in an immediate increase in the plasma drug concentration and therefore an increase of its effects and toxicity, and in an augment of its availability for glomerular filtration. Drugs that did not go through glomerular filtration reach the peritubular capillaries of the proximal tubule and are submitted to the most effective mechanism of secretion of substances into the ultrafiltrate carrier systems consisting of independent and relatively non-selective transporters of organic acids and bases. Unlike glomerular filtration, this mechanism can make the maximum clearance of a substance even when bound to plasma proteins (*e.g.*, penicillin). Thus, substances that may compete for binding to these transporters may result in drug interactions, such as reduced renal excretion of acetylsalicylic acid and methotrexate by competition with probenecid, which may be clinically relevant as in the case of penicillin. In the phenomenon of tubular reabsorption, passive

diffusion of non-ionized lipid-soluble substances from the proximal and distal tubular lumen into the bloodstream occurs, delaying their excretion. Therefore, the intratubular pH influences the excretion of organic acids and bases, since it changes their degree of ionization. This maneuver can be used in poisoning cases, where the increase of pH by sodium bicarbonate accelerates the excretion of drugs with acid characteristics such as barbiturates and acidification accelerates excretion of basic drugs such as amphetamines.

In the elderly, the most important pharmacokinetic alteration found is the deterioration of renal excretion, a consequence of reduced glomerular filtration rate, tubular secretion and renal blood flow (Table 1), resulting in an increased t½ for all drugs that are predominantly eliminated by the kidneys and, therefore, accumulation to toxic levels and incidence of ADRs if there is no limitation of the dose or frequency of administration [21]. There is a gradual process of reduction of renal mass (15-30%) associated with glomerulosclerosis and cortical intracellular hyalinosis as well as a parallel drop in the number of functional glomeruli and tubular secretion [12,13]. Humoral imbalances (*e.g.*, endothelin, angiotensin II, prostaglandins PGE_2 and PGI_2) and significant renal histopathological changes such as the thickening of intrarenal vascular intimal layer and tubular basal membrane, infiltration of inflammatory cells and interstitial fibrosis may restrict the rate of infusion and glomerular filtration rate by 50% [11-14]. This becomes even more relevant because there is evidence that renal dysfunction may negatively affect the activity of biotransformation enzymes [11].

Dose adjustments should be made considering the patient's renal capacity, measured as creatinine clearance. In young patients with stable renal function, serum creatinine levels are indicative of renal function. However, this estimate in the elderly is not appropriate since, in general, creatinine levels are reduced due to the decrease in muscle mass and lower protein degradation [9]. Thus, for predicting creatinine clearance there are some mathematical equations, of which the most widely accepted was described by Cockcroft and Gault (equation 1) [33]. However, these equations are not accurate for assessment in elderly patients and can generate under- [34] or overestimation [35] of glomerular function. Some clinicians suggest that for elderly patients with low creatinine levels (< 1 mg/dL), replacement of the actual value in the equation by 1 mg/dL could be adequate to avoid overestimation of creatinine clearance.

(*equation 1*) Creatinine clearance (mL/min) =

$$\frac{(140 - \text{age}) \times \text{body weight (kg)}\ ^*}{72 \times \text{serum creatinine (mg/mL)}}$$

* the result should be multiplied by 0.85 for women

On the other hand, elderly patients with elevated creatinine levels (> 1.5 mg/mL) should be analyzed with caution because these increased values suggest a significant decline in renal function compared to younger patients. Another alternative for calculating creatinine clearance equation is described in the study Modification of Diet in Renal Disease (MDRD) (equation 2) [36]. Despite its high complexity does not allow a routine calculation of creatinine clearance, it might give more accurate values than the Cockcroft and Gault formula, although it was not extensively tested in elderly patients [37].

(2) GFR = 170 x $[Cr_{serum}]^{-0.999}$ x $[age]^{-0.176}$ x [0.762 for women] x [1.18 for afroamericans] x $[NU_{serum}]^{-0.170}$ x $[Alb_{serum}]^{0.318}$

GFR – glomerular filtration rate, Cr_{serum} – creatinine serum concentration (mg/mL), UN_{soro} – serum concentration of nitrogen urea, Alb_{serum} – albumin serum concentration

As a consequence of the decline in glomerular filtration rate, there is an increased production of prostaglandins, a physiological change which seeks compensatory vasodilation of renal beds. Thus, non-steroidal anti-inflammatory drugs (NSAIDs) may prevent this compensatory mechanism, decreasing renal function. For that reason, the combination of NSAIDs with drugs that are primarily eliminated by the kidneys should be avoided, since they will have their concentrations increased. This kind of interaction is particularly sensitive in the case of drugs with narrow therapeutic index, such as digoxin [38]. In these cases, plasma concentrations should be monitored when NSAIDs are chronically prescribed [3,14].

Therefore, taking into account the decrease in renal elimination that generally occurs in elderly patients, we can conclude that interactions between drugs that are predominantly excreted by the kidneys and drugs that will somehow reduce both glomerular filtration and tubular secretion should be examined with greater caution in the elderly due to greater risk of increased plasma concentration and t½ of these drugs in comparison to young adults, achieving toxic drug levels and higher incidence of ADRs. Interestingly, however, a recent review brought attention to the fact that old age itself has a smaller influence on some pharmacokinetic parameters than what is generally believed, and thus may not be overestimated when considering the pharmacological therapy in aging population [37].

Pharmacological class	Drug	Impaired metabolism	Type of reaction
Analgesics (opioids)	morphine	yes	glucuronidation
NSAIDs	salicylic acid paracetamol	no no	glucuronidation glutation conjugation
Antibiotics	isoniazid	no	acetylation

NSAIDs - Non-steroidal anti-inflammatory drugs

Table 4: Phase II drug biotransformation characteristics in the elderly (modified from Turnheim).

Concluding Remarks

Several pharmacological variables may be altered in the elderly, showing the full complexity of therapy in older age groups and the multiplicity of interactions and ADRs that can arise. Educational measures dealing with both students and professionals of health sciences in order to improve the knowledge of geriatric pharmacotherapy and the conduction of clinical studies in this population and preclinical experimental models are desirable goals and directly influence the performance of therapeutic interventions. Other proposals, such as the development of drug formulations suitable for the elderly, also integrate such a context. Over the past decades, social and scientific-technological advances are providing an ever-growing older society, where old age reaches progressively higher life span. Therefore, every effort is essential so that we can successfully tackle these challenges in the 21st century.

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