

Gender-specific implications for pharmacology in childbearing age and in postmenopausal women

Implikacje leczenia farmakologicznego u kobiet w wieku rozrodczym i po menopauzie

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Abstract

Women have three very important physiological functions that are not observed in men – menstruation, pregnancy, and lactation. Each of these mechanisms influences pharmacokinetics and pharmacodynamics of many drugs. Individualization of pharmacotherapy is a major challenge of modern medicine. The differences in response to drug are responsible for the effectiveness of pharmacological treatment and the occurrence and severity of toxic effects and side effects. Therapeutic decision should be based not only on account of the dose-effect, but the consideration of gender, genetic and environmental differences affecting the final therapeutic effect. Many important differences between men and women like sex-based differences in normal physiology, or in the predisposition to a specific disease, can be due to genetic differences, the actions of the sex steroid hormones or an interaction between these factors. Women generally have a lower body mass, a reduced hepatic clearance, differences in activity of cytochrome P450 (CYP) enzymes (increase in CYP3A4, decrease in CYP2D6, CYP2C19 and CYP1A2) and different from men's rate of drug metabolism. Other important factors contributing to gender differences in the pharmacokinetics of drugs are conjugation, absorption, protein binding and urinary excretion. It still remains unexplained how gender differences affect the increased risk of side effects.

This review is an attempt to assess the biological, physiological and hormonal basis of women differences in the pharmacokinetics and pharmacodynamics of many drugs.

Key words: **pharmacokinetics / pharmacodynamics / cytochrome P450 / adverse effects /**

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Streszczenie

Kobiety charakteryzują trzy niezwykle istotne z punktu widzenia farmakologii procesy fizjologiczne, które nie występują u mężczyzn - menstruacja, ciąża i laktacja. Każdy z tych procesów w znaczący sposób wpływa na farmakokinetykę i farmakodynamikę wielu leków. Indywidualizacja farmakoterapii, również z uwzględnieniem płci, stanowi poważne wyzwanie współczesnej medycyny. Różnice w odpowiedzi farmakologicznej odpowiadają za skuteczność leczenia oraz występowanie i nasilenie efektów toksycznych i niepożądanych. Decyzja terapeutyczna powinna opierać się nie tylko na uwzględnieniu zależności dawka-efekt, ale na rozważeniu różnic płciowych, genetycznych i środowiskowych, wpływających na końcowy efekt terapeutyczny. Szczególnie istotne wydają się różnice płciowe w farmakokinetyce leków wynikające z odmiennej fizjologii, predyspozycji do występowania chorób, uwarunkowań genetycznych czy gospodarki hormonalnej oraz wzajemnych oddziaływań pomiędzy tymi czynnikami. Kobiety charakteryzują się mniejszą masą ciała, obniżonym klirensom wątrobowym i różnicami w aktywności cytochromu P450 (CYP) (wzrost aktywności CYP3A4, obniżenie aktywności CYP2D6, CYP2C19 i CYP1A2) oraz odmienną od mężczyzn szybkością metabolizmu leków. Innymi ważnymi czynnikami wpływającymi na różnice płciowe w farmakokinetyce leków są koniugacja, wchłanianie, wiązanie z białkami i wydalanie z moczem. Nadal pozostaje niewyjaśnione w jaki sposób różnice płciowe wpływają na zwiększone ryzyko wystąpienia działań niepożądanych.

Niniejsza praca stanowi przegląd biologicznych, fizjologicznych i hormonalnych podstaw występowania różnic płciowych w organizmie kobiety, które wpływają na farmakokinetykę i farmakodynamikę leków.

Słowa kluczowe: **farmakokinetyka / farmakodynamika / cytochrom P450 /
/ działania niepożądane /**

Introduction

Women respond to drugs differently than men due to differences in physiology, anatomy, hormonal status, pharmacokinetics, and pharmacodynamics. Numerous clinical observations have reported that females are at a 1.5-1.7-fold greater risk of experiencing an adverse drug reaction to medications than males [1]. Pharmacokinetic parameters are altered in pregnancy and most drugs gain access to the fetoplacental unit. The fact that absorption of many drugs is decreased and elimination increased may have important sequelae for drug dosing and their adverse effects.

The main objective of modern pharmacotherapy is an individual therapeutic approach, based on patient ability to obtain a comprehensive clinical response with minimal adverse effects. Individualization of pharmacotherapy means personal identification of physiological and genetic predisposition and depends on the currently used drugs, environmental conditions, as well as potential interactions resulting from the pharmacodynamic and pharmacokinetic properties of various drugs [1]. Mostly, pharmacotherapy is based on drug dose adjustment based on body weight and history of earlier treatment. Meanwhile, epidemiological studies point to considerable differences between men and women in the prevalence and clinical manifestations of numerous diseases, i.e. depression [2], alcoholism [3], Alzheimer diseases [4, 5] breast cancer [6, 7], and others. Genetics, diet, disease state and gender, which plays an important role in pharmacokinetics, pharmacodynamics, adverse effects and drug toxicity, are of vital importance [8, 9].

As far as personalized pharmacotherapy is concerned, genetic factors, especially genetic polymorphisms – single nucleotide polymorphisms (SNPs), which determine the functioning of ATP-binding cassette transporters (MDR1, MRP1, MRP2, BCRP), drug metabolizing enzymes such as CYP450, and the availability of various drug targets, are essential [9,10]. In order to individualize pharmacotherapy, it is important to take into account polymorphic variants of the genes responsible for drug metabolism and drug transport, as well as to consider gender differences.

Anatomical differences of women in pharmacokinetics and pharmacodynamics

Anatomical differences between women and men are an important aspect of selecting appropriate pharmacotherapy. Differences between women and men include lower range of body weight, higher percentage of body fat, lower average plasma volume, increased organ blood flow, and altered drug/plasma protein binding profile in the former [11]. Gender differences concerning predisposition to a specific disease can occur due to the actions of sex steroid hormones, or interactions between environmental, genetic and hormonal factors [12]. Gender differences influence the absorption and the distribution processes. The length of the esophagus is greater in men than in women, which delays the passage of the drug into the stomach and the release of the active substance in females [13]. Higher percentage of body fat in women may reduce the volume of distribution of lipophilic drugs [14].

Nindl et al. [15], conducted a study which evaluated gender differences in the arm, trunk, and leg for fat mass, lean soft tissue mass, and bone mineral content (BMC). They concluded that men have more of their muscle mass in their arms and women have more of their fat mass in their legs and that gender differences exist in the relationship between somatotrophic hormones and lean soft tissue mass. Sex steroid hormones can influence not only gender morphological differences, but also neuronal functions such as differences in the pain threshold and cognitive style, and greater glucocorticoid response to stressors exhibited by females as compared to males [16]. Cardiovascular functions also differ between men and women, with the former having significantly greater left ventricular mass and chamber size than the latter. Also, the stroke volume is larger in men than in women. Women have lower resting blood pressure and higher resting heart rate, exhibit reduced tolerance to orthostatic stress and impaired venous return, have better cardiac function and survival [17]. Estrogen is believed to play a cardioprotective role, contrary to testosterone which is thought to be detrimental to heart function. Probably, phytoestrogens can also affect cardiac physiology in both, a positive and a negative manner [18].

Table I. Differences in pharmacokinetic parameters between women and men.

Drug	Effect	Pharmacokinetics parameter	References
Acetylsalicylic acid	poorer platelet inhibition and heart attack protection in women; poorer stroke prevention in men, aspirin is cleared more rapidly from women	clearance, half-life	[20]
Beta blockers	enhanced lowering of blood pressure and heart rate during physical activity in women; greater reduction in blood pressure in women due to pharmacokinetic and not pharmacodynamic differences	oral clearance lower in women, lower volume of distribution in women resulting in higher systemic exposure	[21]
Selective Serotonin Reuptake	decreased metabolism by hepatic CYP; enhanced effect in women	plasma concentrations are higher in women	[22]
Ethanol	men metabolize more in first pass metabolism; in addition, the volume of distribution is smaller in women	volume of distribution, clearance, and first-pass metabolism	[23]
Diazepam	larger volume of distribution in women	plasma binding	[24]
Rifampicin	women absorb the drug more efficiently	no data	[25]

Physiological differences of women in pharmacokinetics and pharmacodynamics

Women are generally more sensitive than men as far as pharmacodynamics are concerned, what is caused by the alteration in receptor number, receptor binding and alterations in signal transduction pathways following receptor binding [19].

Some differences in drug effects between men and women are listed in Table I.

Pharmacokinetic parameters exhibit large gender differences, especially in the absorption, distribution, metabolism, mainly in phase I leading by the cytochrome P450 family, and elimination. The rate of absorption depends on many factors, including gastric acid secretion, gastric emptying time, gastrointestinal (GI) blood flow, and surface area, along with the effects of pre-systemic hepatic and gut dissolution rate of the active substance in body fluids, particle size and pH of the environment, and also gender [26]. Numerous clinical studies confirm the existence of gender differences in drug absorption and bioavailability of certain drugs [27]. Oral absorption is the first step when the rate and extent of drug absorption is assessed [1]. Orally administered verapamil is cleared faster in men than women, a difference that is not observed after intravenous (IV) administration of this drug, suggesting that intestinal processes modulate gender-specific differences in verapamil pharmacokinetics [28]. Gastric acid secretion is reduced in women, especially before menstruation, resulting in less absorption of weak acids drugs [29]. Passage of the gastric content from the stomach to further sections of the gastrointestinal tract is slower in women, causing delayed absorption in the intestine and subsequent attainment of maximum drug concentration in blood [30].

In addition, the gastric emptying rate decreases just before menstruation by about 30% [31], and the transit time of food through the bowel is higher in women, which can affect the increase in the amount of the active substance that is absorbed [32]. Absorption in the small intestine in the luteal phase is extended due to the relaxation effect of progesterone on smooth muscle [14]. Also, lower activity of P-glycoprotein in the intestine of females shortens the transit time of the active substance through the gut, which results in a decreased activity of CYP3A and lower blood concentrations of active substances [30]. Moreover, reduction of first-pass effect in women as compared

to men was observed, caused probably by testosterone which increases CYP2D6 expression in men [33].

Drug distribution also depends on multiple factors, including body mass index (BMI), body composition, plasma volume, organ blood flow, and the extent of tissue and plasma protein binding of the drug [27]. Distribution differs between men and women due to gender differences in body fat percentage, and the fact that lipophilic agents may have a relatively greater volume of distribution and water-soluble compounds, which may exhibit a relatively lower volume of distribution in females as compared to males. It has been shown that water retention occurring before menstruation can reduce the concentration of hydrophilic drugs through their dilution [22]. For example, a larger volume of distribution for diazepam has been observed in females as compared to males. Apart from physical differences between men and women, resulting in disparities in drug distribution, differences in plasma protein binding by gender may theoretically lead to differences in pharmacokinetic parameters for certain agents, for example albumin and globulins [34].

Gender differences are noticeable particularly in the case of drug metabolism and the activity of enzymes involved in the process, so drug metabolism seems to be the most dependent on gender among all pharmacokinetic parameters [27]. Metabolism (biotransformation) of drugs is a biochemical process of drug transformation in the body. This process occurs mainly in liver microsomes, which contain the active enzymatic systems. The activity of these enzymes depends on many factors, such as body temperature, gender, age, and pathological conditions, including hepatic parenchymal disease. Metabolic reactions involving enzymes occur to a lesser extent also in the mucosa of the gastrointestinal tract, the skin, and the placenta. Biochemical reactions associated with drug metabolism occur in two phases. Phase I reactions include oxidation, reduction, and hydrolysis and are mediated through the cytochrome (CYP) P450 system. Phase II reactions involve glucuronidation, sulfation, acetylation, or methylation of the parent drug or its Phase I metabolite to form polar conjugates for renal excretion. Differences in drug metabolism between man and women have been extensively investigated [26]. Gender differences particularly concern prominent cytochrome P450 enzymes, including CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP2E. (Table II).

Table II. The most important transcription factors responsible for regulating the expression of selected genes involved in metabolism and transport of drugs.

Transcription factor	Protein involved in heterodimer formation	Exemplary ligands	Regulated genes
CAR (constitutive androstane receptor)	RXR	phenobarbital, androstenediol, polychlorinated biphenyls	CYP2B, CYP3A, CYP2C9, GST, SULT, UGT, MDR1
PXR (pregnane X receptor)	RXR	phenobarbital, dexamethasone, pregnenolon, corticosterone, bile acids	CYP3A, CYP2B, SULT, UGT, MDR1, MRP1, MRP2, Oatp2
AhR (aryl hydrocarbon receptor)	ARNT	dioxins, PAHs, bilirubin	CYP1A, CYP1B, GST, UGT
HNF4 (hepatocyte nuclear factor 4)	-	fatty acid derivatives	CYP2A, CYP2C, CYP2D, CYP3A
HNF1 (hepatocyte nuclear factor 1)	-	not defined	CYP1A2, CYP2E1

Differences associated with the activity of these enzymes are mainly due to endogenous sex hormone production, as well as hormonal changes associated with oral contraceptive use, pregnancy, and menopause [35]. CYP3A4 enzymes that are responsible for the metabolism of more than 50% of drugs are about 1.4 times more active in women than in men, due to the action of estrogen and progesterone, which are competitive inhibitors of this enzyme. Hormones present in oral contraceptives may inhibit CYP3A4 enzyme [36]. Furthermore, women have a less active CYP2E1 and CYP1A2 as compared to men [21]. Differences also take place at the stage of phase II biotransformation of xenobiotics, i.e. transferase activity of UDP-glucuronide and glycine are higher in men [20].

The last pharmacokinetic parameter is drug elimination. Generally, drugs are eliminated from the body by the renal, hepatic and pulmonary routes. Gender differences in drug elimination concern especially renal clearance of drugs, which on average is higher in men than women. There are also sex hormone differences between males and females responsible for disparities in renal secretion for organic anions, for example amantadine, an organic cation requiring secretion by the kidneys, has increased renal clearance in men as compared to women [37]. Physiological gender differences and their influence in pharmacokinetics are presented in Table III.

Hormonal fluctuations in women influence pharmacokinetics and pharmacodynamics

Sex steroid hormones, such as androgens, estrogens, and progestins, influence the body composition and can alter pharmacokinetic parameters throughout interaction with their receptors in heart, bone, skeletal muscle, vasculature, liver, immune system, and brain [38]. For example, hormone fluctuations during the menstrual cycle and pregnancy can change plasma volume and organ flow [39].

There are numerous examples supporting the contention that female sex hormones impact drug-metabolizing pathways. It has been shown that estrogen binds and modulates membrane ion channels and receptors, such as cardiac ATP-K⁺ cardiac channels and opioid receptors [40]. Due to the fact that estrogen is a substrate for two enzymes: CYP3A4 and CYP1A2, antidepressant metabolism may be significantly impacted during the late luteal phase of the menstrual cycle or with estrogen replacement therapy [41].

The menstrual cycle is characterized by changes at the level of sex hormones. These changes directly affect the metabolism because they are associated with the activation of specific hepatic enzymes and the rate of clearance of certain drugs. For example, caffeine and theophylline clearance is higher during the early follicular phase and prolonged during the mid-luteal phase [42]. Several literature reports have confirmed that hormonal fluctuations during the menstrual cycle influence drug metabolism, but some authors concluded that there are no differences in drug metabolism with regard to the menopausal status and the menstrual cycle [43, 44].

Differences in drug metabolism are also caused by hormone fluctuations during menopause [44,45]. Data on whether the menopausal status or the estrogen and progesterone levels in HRT significantly affect drug metabolism in women are inconsistent and conflicting.

The gestation period is characterized by a series of physiological changes that directly and indirectly affect the pharmacokinetic parameters such as absorption, distribution, or elimination [46].

Changes in the level of progesterone during pregnancy contribute to, inter alia, reduced gastric emptying, small intestine motility, and increased gastric pH. The effect of these changes can be increased C_{max} and T_{max} , which in turn can lead to reduced efficacy of a single dose of an oral drug. Symptoms of nausea and vomiting during early pregnancy are a more practical aspect of drug absorption, which can be minimized [47].

Changes during pregnancy also apply to the distribution process. They result from an expansion of the intravascular (plasma volume) and extra-vascular (breasts, uterus, peripheral edema) water content, increased V_d , and a decrease in C_{max} of many hydrophilic drugs. There have also been changes in protein binding caused by steroid and placental hormones that displace drugs from their protein-binding sites. Estrogen and progesterone influence the induction of some enzymes of the hepatic cytochrome P-450 system, resulting in a higher rate of drug metabolism. Elimination of drugs alters during pregnancy as well, the glomerular filtration rate rises by 50%, leading to enhanced elimination of drugs [46]. Numerous physiological changes occur during pregnancy, which in turn may affect the pharmacokinetics of drugs. These changes concern body weight and body fat, delayed gastric emptying and prolonged gastrointestinal transit time, increased extracellular fluid and

Table III. Physiological differences of women and their influence in pharmacokinetics.

Pharmacokinetic parameter	Physiology parameter/process	Physiology differences	Influences on pharmacokinetic	References
Drug absorption	gastrointestinal tract physiology	1). Gastric emptying time is slower in females than males 2). Acidity of gastric pH: male>female>pregnant 3). Gastric fluid flow in men > women 4). Intestinal motility: male>female>pregnant	1). Decreased absorption and gastric hydrolysis in women 2). Altered absorption of acid/bases depending on specific drug ionization. In pregnancy – decreased absorption of weak acids 3) Slower absorption in women 4). Slower absorption in women	[26]
	Extrusion by drug transporters, such as intestinal p-gp	Intestinal p-gp levels do not consistently seem to vary by sex.	Transport does not consistently seem to vary by sex.	
	Dermal conditions, structures	1). Dermal hydration increased in pregnant women 2). Dermal thickness increased in men 3). Skin blood flow increased in pregnant women	1). Altered absorption in pregnant 2). Absorption increased in women 3). Absorption increased in pregnant	[1]
	Other physiology parameters	Body surface area, cardiac output, pulmonary function: men>pregnant>female	Absorption is the highest in men	
Distribution	Body composition: body mass index, percent of body fat, plasma volume, and organ blood flow.	Women – lower body weights and lower BMI than men; women - a higher proportion of body fat than men; plasma volume is greater in men than women, although volume varies throughout the menstrual cycle and during pregnancy; organ blood flow is greater in women than men.	Implications for disparities in the rate and extent of drug distribution in women, a relatively lower volume of distribution in females compared to males, the faster onset of action and prolonged duration of neuromuscular blockade in females with lipophilic paralyzing agents	[26]
	Protein binding: extent of tissue and protein binding of the drug.	Women have lower concentrations of alpha-1 acid glycoprotein than men, exogenous estrogens increase levels of the serum-binding globulins.	In women: lower levels of plasma binding proteins - lower free fraction of drugs – active form of the drug.	
Metabolism Phase I	Hepatic transporters: hepatic p-gp or MDR1.	Men - higher hepatic p-gp levels than women	Higher rates of drug clearance in women versus men for drugs that are substrates of p-gp.	[26]
	Basal metabolism	Basal metabolism rate: man > women	CYP1A1 and CYP2A1 – more active in men than women, CYP3A4 – higher activity in women	[1]
Excretion/elimination	Renal function	Glomerular filtration, passive diffusion, active secretion: men > women	Kinetics of PAH showed a shorter elimination half-time in males than in females	

total body water, which can affect water-soluble drug kinetics, increased cardiac output as a result of increased stroke volume and maternal heart rate; higher blood flow to the organs, lower albumin concentration with decreased protein binding, affecting drugs that are highly protein bound, and altered hepatic enzyme activity, which can change drug metabolism, and interactions [48]. Fluctuations of sex hormones during pregnancy influence the pharmacokinetic processes of drug absorption, distribution and elimination. Increased levels of estrogen and progesterone during pregnancy alter hepatic enzyme activity, which can increase drug accumulation or decrease elimination of some drugs [49].

Gender differences in adverse reactions (ADR)

Several clinical trials have shown that female gender is a risk factor for clinically relevant adverse drug reactions [50]. Rademaker observed that women have a 1.5- to 1.7-fold greater risk of developing ADR, including adverse skin reactions, as compared to male patients. This author concluded that women are at a greater risk (50-70% higher) of experiencing drug-related side effects than men [51]. Montastruc et al., investigated putative

gender-related differences in adverse drug reactions (ADRs) and observed that the incidence of DRs was 53.1% higher in females but the values in men were not statistically significant. Moreover, ADRs in females were reported for some classes of drugs: genitourinary, sex hormone, antineoplastic, anti-parasitic and respiratory [52]. Soldin and Mattison suggested that gender differences in adverse events depend on gender differences in volume of distribution, protein binding of drugs, transport, phase 1, and phase 2 metabolism, and drug targets (receptor number, receptor binding, signal transduction following receptor binding) [1]. These authors concluded that women are more sensitive because they are prescribed multiple medications and they often overdose. They also observed that females suffer from a greater number of adverse events, such as neuropathy, pancreatitis, and toxicity-driven regimen changes on nucleoside reverse transcriptase inhibitors (NRTIs), as compared to men [53]. Gender differences in adverse effects were also observed in case of psychotropic drugs, such as antipsychotics, antidepressant and mood stabilizers [54]. A higher frequency of antiretroviral-related adverse effects among women as compared to men has been also described.

Female gender is probably at higher risk for lactic acidosis, nevirapine-associated rash and hepatotoxicity occurrence, and fat redistribution after highly active antiretroviral therapy exposure [55]. There are many theories concerning the mechanisms of gender differences in antiretroviral toxicity and side effects. Some authors postulated that differences in weight and body mass index between men and women may play a crucial role [56]. Another suggested mechanism explaining gender differences in drug toxicity and side effects is hormonal disequilibrium in women at puberty, during the menstrual cycle and menopause, and the effect of these changes on drug metabolism [57]. Among many postulated mechanisms explaining gender differences in ADR and drug toxicity, levels of various enzymes involved in drug metabolism may also play a role.

Nutrition gender differences in pharmacokinetics

Diet plays a vital role in the success of pharmacotherapy due to the fact that many dietary factors can alter the rate of drug metabolism throughout alteration of gastric pH, gastric emptying time, intestinal motility, mesenteric, hepatic portal blood flow or biliary flow, or enzyme activity and protein transport in the gut. In consequence, diet can change the rate and extent of drug absorption [58], and the expression and activity of hepatic drug-metabolizing enzymes [59]. Kappas et al., concluded that the rate of drug metabolism can be accelerated by drugs themselves or by a variety of dietary factors, such as protein supplementation or inclusion of cruciferous vegetables or charcoal-broiled meats in the diet. These authors also postulated that low-protein, high-carbohydrate diet, and various vitamin and mineral deficiencies can reduce the levels of drug metabolizing enzymes and, consequently, the rate of drug metabolism, so that serum drug concentrations decline much more slowly, resulting in increased drug potency [60].

There are several scientific reports showing the existence of gender differences concerning eating behaviors. Women more often than men pay attention to healthy diet by avoiding high-fat foods, eating fruit and fiber, and limiting salt (to a lesser extent) [61]. Dietary differences between man and women influence pharmacokinetic and pharmacodynamic properties of drugs [62]. Some examples concern the role of carbohydrates in drug metabolism. Data on interactions between carbohydrates and certain drugs are conflicting. Some authors claim that high carbohydrate diet may induce the expression of several glycolytic and lipogenic hepatic enzymes, while other researchers suggest that carbohydrates have little impact on drug metabolism [63].

Generally, diet is very important as far as oral administration of medications is concerned, especially for drugs co-administered with foods. Food can increase, decrease, or have no effect on the absolute systemic availability of a medication [64]. Given the fact that women use a different diet than men, nutritional differences between men and women ought to be taken into consideration when establishing pharmacotherapy.

Conclusions

There is enough evidence to conclude that women differ from men in terms of pharmacokinetics of drugs. In general, higher plasma levels are reached in women as compared to men, mainly due to differences in the volume of distribution, content of body water, and clearance due to renal flow and metabolic activity.

Noteworthy, many molecular factors connected with treatment results, including genetic polymorphisms of drug transporters and drug-metabolizing enzymes, differ in women and men. Various authors suggest that female gender is a risk factor for adverse effects in clinical practice. Thus, it is necessary to formulate proper therapeutic goals and establish adequate therapeutic procedures before treatment commencement in females.

Dedication

This publication is dedicated to the memory of Professor Przemysław M. Mrozikiewicz.

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