Published in final edited form as:
Clin Pharmacokinet. 2009 ; 48(3): 143–157. doi:10.2165/00003088-200948030-00001.

Sex Differences in Pharmacokinetics and Pharmacodynamics

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Abstract

Males and females differ in their response to drug treatment. These differences can be critical in response to drug treatment. It is therefore essential to understand those differences to appropriately conduct risk assessment and to design safe and effective treatments. Even from that modest perspective, how and when we use drugs can result in unwanted and unexpected outcomes. We summarize the sex differences that impact pharmacokinetics and pharmacodynamics and include a general comparison of clinical pharmacology as it applies to men, pregnant and non-pregnant women. Since this is an area rapidly evolving, it is essential for the practitioner to review drug prescribing information and recent literature to understand fully the impact of sex differences in clinical therapeutics.

Keywords

sex differences; gender differences; gender specific/pharmacology; drugs in pregnancy; pharmacokinetics; pharmacodynamics; adverse drug events

1. Introduction

The goal of clinical pharmacology is to understand how to optimize the use of drugs in order to minimize therapeutic adverse event and enhance therapeutic effectiveness. Both can be achieved by understanding the pharmacokinetics (PK) and pharmacodynamics (PD) in the diverse populations in which the drugs use is intended. Circulating drug concentrations are affected by a combination of factors and determine the resulting outcome[1]. The relationship between dosing and effect is more variable than the relationship between concentration and effect. Therefore, a focus on understanding and achieving therapeutic drug concentrations should utilize our knowledge of sex differences in drug PK/PD.

The main enzymes involved in drug metabolism belong to the cytochrome P450 (CYP) group. These are a large family of related enzymes housed in the smooth endoplasmic reticulum of the cell. The CYP isoenzymes discussed in this article are all coded for by autosomal chromosomes. It is plausible that sex-related disparities in pharmacokinetics arise

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CONFLICT OF INTEREST
The authors have no conflict of interest.

due to variations in the regulation of the expression and activity of CYP isoenzymes, most probably through endogenous hormonal influences

1.1. Gender differences vs. sex differences

Sex is the property or quality by which organisms are classified as female or male on the basis of their reproductive organs and functions, while gender is expressed in terms of masculinity and femininity. It is how people perceive themselves and how they expect others to behave, and is largely culturally determined.

As our knowledge of medicinal drug toxicology and pharmacology is expanding it has become clear that men and women differ in response to drug treatment. Women also differ from men in response to occupational exposures[2, 3]. This is the result of the physiological differences such as body weight, length, surface area, total body water, extracellular and intracellular water (Table I) as well as differences in PK/PD.

1.2. General background

Based on reviews of the Adverse Events Reporting System (AERS), the United States Food and Drug Administration (US FDA) has suggested that women experience more adverse events than men, and those adverse events are more serious in women. The U.S. General Accounting Office (GAO) reviewed the 10 drugs withdrawn from the market during the period January 1, 1997 through December 2000 and observed that 8 of the 10 were withdrawn because of evidence of greater risks of adverse effects in women.

Table II provides a comparison of some of the suggested reasons for sex differences in adverse event frequencies. Accordingly, it is plausible that given the sex-related differences in pharmacokinetics, women are more frequently overdosed than men. This implies that at a given dose a drug reaches higher free drug concentrations or remains longer in the body in females than in males. Alternatively, females may be more sensitive to drugs than males. In this instance, free drug concentrations and duration in the body would be similar in men and women but women would respond to a greater extent. Yet, another plausible explanation might be attributed to behavior; if women take a greater number of medications than men they can increase the incidence of adverse events resulting from drug interactions.

Typical drug interactions are due to alterations in PK – in this instance the consequence would be an increase in the free drug concentration or a decrease in the rate of drug clearance. An additional reason for higher rates of adverse events reported in women may be due to higher reporting rates from women than men. Finally, it is also possible that sex differences between men and women result in similar rates of adverse events but women experience more severe events.

1.3. FDA regulations on inclusion of women in clinical trials

FDA regulations and guidance are in place to ensure that both sexes are represented in all phases of clinical trials, and that medical products are labeled to alert physicians and patients to any difference in the way men and women respond to a product. In 1993, the FDA issued its Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs (the “Gender Guideline”) that recommended separate analysis of men’s and women’s responses to drugs. In 1999, the National Institutes of Health (NIH) published the “Agenda for research on Women’s Health for the 21st century” - a six volume report which concluded with the observation that there are gaps in knowledge regarding drug behavior in women (vs. men), and that gender-related differences in drug pharmacokinetics and pharmacodynamics must be assessed.

In 2001, the Institute of Medicine (IOM) of the National Academy of Sciences published a report concluding that “sex matters.” More specifically, that “being male or female is an important basic human variable that should be considered when designing and analyzing studies in all areas and at all levels of …health-related research.” The IOM defined sex-based differences as biologically based differences in men and women, and defined gender-based differences as distinctions shaped by the cultural and social environment. The report supported studying potential sex differences during drug development.

Unfortunately, substantial gaps still remain in the inclusion of women in clinical studies. As a result, care givers are often left having to estimate the appropriate dose, dosing schedule and treatment interval without or with only modest knowledge of the appropriate use of the drug or their drug of choice in pregnant women or women in general.

2. SEX DIFFERENCES IN PHARMACOKINETICS

2.1. DRUG ABSORPTION

The factors influencing absorption are route-specific (oral, dermal, rectal, vaginal, intramuscular, intravenous, intraarterial, intrathecal, intraperitoneal) and may also be sex-specific. Chemicals or drugs cross body surfaces such as the gastrointestinal tract, respiratory tract, or skin (different in males and females) to enter the systemic circulation.

The absorption rate and extent of a drug are drug-specific. Examples of drugs that illustrate sex differences in drug absorption include rifampicin, benzylamine and IM cephradine[4–6].

In general oral drug administration is the route of choice in the daily practice of pharmacotherapy, and especially in outpatient setting. Ingestion, food interactions (e.g. grapefruit juice), gut motility and transit time, gut pH, biliary secretion and gut flora (enterohepatic circulation and impact oral contraceptives) can have major influence on specific drug absorption. It has been hypothesized that women, by virtue of having greater subcutaneous lipid content, receive different doses of transdermally administered drugs. Women may also take in less of inhaled aerosol drugs such as ribavirin and cyclosporine, although only limited data are yet available.

2.1.1. Gastric Enzymes—Gastric alcohol dehydrogenase activity is higher in males than in females[7]. As a result, women have a lower alcoholic toxic threshold than men and develop alcoholic liver injury more rapidly[8]. In addition, estrogens have a major influence on the susceptibility of Kupffer cells to gut-derived lipopolysacharride differences in gastric first-pass metabolism, elimination rate, or alcohol distribution volume. The enterocytes express significant levels of CYP3A isoenzymes which contribute significantly to the first pass metabolism of many orally administered drugs and have known sex differences.

2.1.2. Transporter proteins—Multi-specific transporters are involved in hepatobiliary and urinary excretion. Tissue distribution and elimination pathways of drugs are explained by the similarity and differences in the substrate recognition by transporters expressed in the liver and kidney. Variability in intestinal expression of enzymes that modulate gut transport of drugs may result in sex-based variability in plasma drug concentrations. For example, p-glycoprotein (PGP), (membrane ATPase transporter protein found in high concentrations in the enterocytes of the small intestine) is encoded by the multi drug resistance transporter-1 gene (MDR1) expressed in the human intestine, liver and other tissues[9]. Complex relationships between intestinal transporters such as H+/di tripeptide transporter (PEPT1), organic anion transporting polypeptide (OATP) and other unidentified ones facilitate drug absorption, while efflux transporters such as PGP sometime work as drug absorption barriers[10].

2.1.3. Enterohepatic and renal handling of drugs or metabolites—Cardiac output (CO) and regional distribution of blood flow are two important parameters that impact pharmacokinetics, especially absorption. Because CO is related to body size it is best normalized to surface area; when normalized, men and women have similar mean cardiac indices of 3.5 L/min/m^2.

Gastric fluids differ between men and women; gastric fluid is more acidic in males than females (pH=1.92 vs. pH=2.59), basal and maximal flow of gastric fluid and acid secretion is higher in men than women (reduced by 30% in pregnancy). Reduced pH results in decreased absorption of weak acids and increased absorption of weak bases. Drug absorption occurs at different sites along the gastrointestinal tract including stomach, small and large intestines.

The rate of absorption is influenced by multiple factors, including gut transit times, lipid solubility of the agent, pH at the site of absorption, ionization and molecular weight of the agent, and gut motility. Transit times differ significantly in men and women[11]; mean transit times being shorter in men (44.8 hrs) than in women (91.7 hrs). While fiber ingestion decreases the transit time, female gut transit times are consistently longer.

The kidneys are responsible for the maintenance of water and electrolyte balance, the synthesis, metabolism and secretion of hormones, and for excretion of waste products from metabolism as well as most drugs, hormones, and xenobiotics. The human kidney demonstrates sex-related differences in the subunits of glutathione-S-transferase isoenzyme (GST) [12].

Iron and ethanol are two important chemicals that have significant differences between males and females in gastrointestinal absorption (summarized in Table IV). Men metabolize ethanol more rapidly in the gut making ethanol less available for absorption. In pre-adolescent males and females, 45% of ingested iron was incorporated into erythrocytes by females compared to 35.2% among males (ISD −0.78).

2.2. Distribution

Once absorbed, most drugs bind to plasma proteins specific for some aspect or structural feature of the drug. The distribution of a drug is affected by multiple body composition parameters (Table V). Sex-differences in these parameters may account for differences in the concentration of a drug at the target site and result in varying responses. On average, total body water, extracellular water, intracellular water, total blood volume, plasma volume, and red blood cell volume are greater for men than women. Therefore, if an average male and an average female are exposed to the same dose of a water soluble drug, the greater total body water, plasma volume, extracellular water, and intracellular water will increase the volume of distribution thus decreasing drug concentration. As an example, the smaller volume of distribution for ethanol in women than men produces higher peak concentrations from the same dose (Table IV).

Regional blood flow can impact pharmacokinetics; The reference values for resting blood flow to organs and tissues for typical 35y males and females show significant differences for resting blood flow as a percentage of CO to skeletal muscle (greater for men) and adipose tissue (greater for women). These differences may reflect sex-based differences in the percentage of total body mass represented by each tissue[13].

The main binding proteins for various drugs in plasma are albumin, alpha-1 acid glycoprotein (AAG) and alpha globulins. AAG levels and AAG-glycosylations vary in association with endogenous and exogenous estrogen inducing hepatic glycosylation of

these proteins thus decreasing plasma AAG levels, while albumin concentrations do not consistently vary by sex[14]. Estrogens also increase the levels of the serum-binding globulins (sex-hormone binding globulin, corticosteroid binding globulin, and thyroxine binding globulin) [15]. Sex-related differences in plasma binding of selected compounds are listed in Table VI. Variations in levels of plasma binding can alter the free (active) fraction of drugs.

2.2.1. Body fat composition—Body fat as a percentage of total body weight is higher in women than men and increases by age in both sexes[16]. The total body fat for an adult reference male is 13.5kg, 16.5kg in female (19.8kg at 40 week's gestation) [17]. The larger proportions of body fat in women, and especially in pregnant women, may increase the body burden of lipid-soluble, slowly metabolized toxicants. Differences in body fat and in organ blood flow in women have been implicated in the faster onset of action and prolonged duration of neuromuscular blockade in women (e.g. vecuronium and rocuronium) [18, 19]. Differences in body fat content and in protein binding are responsible for sex-related pharmacokinetic differences in the distribution of diazepam[20].

2.2.2. Cardiac output—Cardiac output (CO) and regional distribution of flow are important for pharmacokinetics. CO is commonly standardized and reported as the cardiac index (CI). When standardized for body surface area (BSA), CI is nearly identical for both sexes (18–44y). The distribution of CO, or regional blood flow, is similar for men and women for some organs (adrenal 0.3%, bone 5%, brain 12%, lung 2.5%, skin 5% and thyroid 1.5%) and different for others (adipose M=5%, F=8.5%; heart M=4%, F=5%; kidney M = 19%, F=17%; liver M=25%, F=27%; and muscle M = 17%, F =12%) reflecting sex-based differences in body composition[21].

2.3. Sex differences in pharmacokinetics: Drug Metabolism

Drug metabolism and biotransformation occurs predominantly in the liver, as well as in extra hepatic sites of metabolism such as the lung, kidney, intestinal tract, and skin (Table VII). During pregnancy, biotransformation can also occur in the placenta and in fetal tissues. Lipid solubility, protein binding, dose, and route of exposure all affect the rate of biotransformation.

Despite the large variations in drug metabolism in individuals, correcting for height, weight, surface area and body composition eliminates most "sex-dependent" differences. However, sex-dependent differences in biotransformation have been observed for a few specific drugs such as nicotine, chlordiazepoxide, flurazepam, acetylsalicylic acid, and heparin[22, 23].

Hepatic clearance of drugs is a function of liver blood flow and hepatic enzyme activity. Although CO and hepatic blood flow are lower in women than in men normalized per m^2/kg, sex differences in hepatic enzymes play a major role in determining sex-related pharmacokinetic activity.

2.3.1. Hepatic metabolism—Ingested compounds may remain unchanged (and possibly accumulate in a storage compartment), or, based on their degree of lipophilicity and polarity, be subject to metabolism. Hepatic drug metabolism is divided into two, usually sequential enzymatic reactions: Phase I and Phase II reactions. Some of the CYP450 enzymes show clear sex-related differences (Table VIII). In general, lipophilic compounds have a tendency to pass through biological membranes and/or be stored, and are often susceptible to phase I types of metabolism.

Sex-related differences have been shown in the pharmacokinetics of CYP450, with a higher activity in females for CYP3A4 and CYP2D6 (Table VIII) [24]. However, even if there are

sex-differences in drug pharmacokinetics, only some drugs have shown significantly higher plasma concentrations in women. A comprehensive review of second-generation (atypical) antipsychotics (SGAs) concludes that sex differences in adverse effects have not been well studied, but some adverse effects such as weight gain, hyperprolactinemia and cardiac effects are particularly problematic for women[25]. Most studies reviewed indicate that clozapine and olanzapine are associated with greater bodyweight gain than other atypical antipsychotics, and that serious adverse effects such as metabolic syndrome, which includes increased visceral adiposity, hyperglycemia, hypertension and dyslipidaemia induced by SGAs, are more frequent in females. Although women are at a lower risk of sudden cardiac death, they have a higher risk of induced long QT syndrome from antiarrhythmic and, probably, antipsychotic drugs.

Metabolism of chemicals may be estimated by basal metabolic rates (BMR). For all ages, on average, men have a higher BMR than women. Since the metabolism of adipose tissue differs from that of muscle tissue, some of the differences between men and women are attributed to body composition metabolism of adipose tissue[26]. Lower BMR per unit body surface area reflects the reduction of lean body mass in women due to a smaller skeletal muscle component[27]. During pregnancy, the altered hormonal milieu is associated with changes in hepatic and extrahepatic drug metabolism[28].

2.4. Sex differences in Drug metabolism: Elimination

Two processes, metabolism and elimination, are responsible either separately or together for drug inactivation; without these means drugs would continuously circulate throughout our bodies, bind to various receptors, and interrupt important physiological processes. Drugs are generally eliminated from the body by renal, hepatic, or pulmonary routes. Consequently, drugs may be eliminated from the body in sweat, tears, breast milk, expired air, and the most common routes are via feces and urine.

Renal function is important for elimination. Chemicals can be excreted into the urine through glomerular filtration, passive diffusion, and active secretion. Increases in renal blood flow and glomerular filtration will increase the elimination rate of drug cleared by the kidneys. When standardized for body surface area, renal blood flow, glomerular filtration, tubular secretion, and tubular reabsorption are all larger in men than nonpregnant women (Table IX) [29, 30]. During gestation, changes in renal blood flow, glomerular filtration rates (GFR), hepatic blood flow, bile flow, and pulmonary function may alter maternal elimination of a drug. Maternal renal plasma flow increases from 500 to 700 ml/min/1.73 m^2, a 1.44-fold increase over the nonpregnant female value and a 1.1-fold increase over the male value. The GFR also increases during pregnancy. At the beginning of gestation, GFR is approximately 100 ml/min/1.73 m^2. By 20 week's gestation, the GFR usually increases to approximately 150 ml/min/1.73 m^2, a 1.5-fold increase over the nonpregnant female value and a 1.2-fold increase over the male value[31].

Drug volume of distribution and elimination rates interact to modify the concentration of a toxicant in pregnant women during gestation. There is a paucity of data regarding the impact of changes in pulmonary and hepatic function on elimination. As a result of the increase in minute volume, the amount of inhaled toxicants significantly increases. These same increases in pulmonary function during pregnancy may also increase pulmonary elimination. However, it is unknown whether these postulated increases in pulmonary elimination are sufficient to override the increase in pulmonary absorption.

3. Sex differences in pharmacodynamics

The kidney is the major organ of drug excretion of either the parent drug compounds or drug metabolites. There are known sex differences in all three major renal functions – glomerular filtration, tubular secretion and tubular reabsorption. Renal clearance is generally higher in men than in women.

For cortisol there appear to be significant sex differences in pharmacodynamics, with women more sensitive to cortisol suppression, they may also be more sensitive to the effects on basophils and helper T lymphocytes. This is interesting because of the balance in sex differences in both pharmacokinetics and pharmacodynamics suggesting that men and women should receive the same dose and treatment schedule.

4. Sex-specific conditions that impact pharmacokinetics and pharmacodynamics (oral contraceptives, pregnancy, menopause)

Increased levels of estrogen and progesterone alter hepatic enzyme activity, which can increase drug accumulation or decrease elimination of some drugs. Female steroid hormones and prolactin play a role in autoimmunity. Regulation of immunity by and interactions between the hypothalamic-pituitary-adrenal (HPA) and hypothalamic-pituitary-gonodal (HPG) axes contribute to the two- to tenfold incidence and severity of autoimmune/inflammatory diseases in females compared to males. Most autoimmune diseases are detected in females of childbearing age. Metabolic changes can also depend on hormone levels that change during the menstrual cycle, with use of oral contraceptives, throughout pregnancy, or during menopause. For example, some asthmatic women have worsening in symptoms before or during menstruation. An increase in oxidative stress has been described during intensive physical exercise. Gender differences have been recorded in oxidative stress, especially at older age.

However, although sex-hormones are thought to play a dominant role in modulating sex-based differences in pharmacokinetics, studies to examine this have yielded conflicting results. Midazolam clearance (reflecting CYP3A4 metabolic activity) failed to show fluctuations during the menstrual cycle [32]. Similarly, studies of eletriptan (to treat migraine) demonstrated no sex-related or menstrual cycle related differences [33].

4.1. Pregnancy

Several physiological changes that occur during gestation are known to affect drug plasma levels. Physiologic changes during pregnancy affect drug PK. These include: a. Volume of distribution: increased plasma volume and increases in extracellular fluid space and total body water; b. Cardiovascular: plasma volume expansion, increase in CO, regional blood flow changes (increased uterine, renal, skin and mammary blood flow, decreased skeletal blood flow), increase in stroke volume (early pregnancy), increase in heart rate (later in pregnancy); c. Respiratory changes: compensated respiratory alkalosis, lowered PaCO2, pH-7.44; d. Binding Proteins - Decreased plasma albumin; e. GI Absorption changes. Prolonged gastric evacuation time, by 30–50%; f. Metabolism – liver CYP450 enzyme changes; e.g. Uridine diphosphate glucoronosyltransferase (UGT) isoenzyme changes; h. Increased renal blood flow; increase in GFR[34, 35].

4.2. Menopause

Conflicting data exist on the pharmacokinetic changes in women relating to menopausal status. To examine menopause-related alterations in intestinal or hepatic CYP3A4 activity several studies compared the pharmacokinetics of midazolam, erythomycin and

prednisolone clearance in pre- and post-menopausal women and found no significant differences in drug metabolism by menopausal status[36].

4.3. Use of Data in Pharmacokinetics and Pharmacodynamics

Data acquired on sex differences in absorption, distribution, metabolism and elimination allows exploration of sex differences in disposition and response to chemicals and drugs. Several examples will be reviewed to illustrate the relevance of the data. Results from clinical trials the focused on HIV-infected female subjects suggest that there are clinically relevant sex-related differences in the efficacy and safety of drug treatment[37].

5. DISCUSSION AND CONCLUSIONS

Males and females may differ in specific drug pharmacokinetics and pharmacodynamics. It is therefore essential to understand those sex differences in drug response as they may affect drug safety and effectiveness. To minimize therapeutic adverse events clinicians must establish clear therapeutic goals for the drugs of choice prior to treatment of women. It must be determined if the treatment should be assessed by clinical signs and symptoms or by laboratory test results -- will drug toxicity be evaluated by clinical or laboratory assessment and what determines the appropriate duration of treatment. Furthermore, one should be aware of and understand the principles of clinical pharmacology as they apply to the drug of choice. In particular, the relationship between drug concentration and desired biological effect at the site action, the mechanism of action of the drug and the impact of the chosen drug on the patient's signs, symptoms and laboratory tests.

In the case of women during pregnancy, special attention should be paid to drugs known to behave differently in pregnancy. Pregnancy-induced changes in drug pharmacokinetics (i.e., in drug absorption, disposition, metabolism, and elimination), when significant, may guide changes in dosage regimen or therapeutic monitoring to increase its effectiveness or reduce potential toxicity. Given those parameters, and our knowledge of sex differences, we can derive essentially all factors necessary for therapeutic optimization.

In general, data on sex differences are mostly obtained by *posthoc* analysis and, therefore, the conclusions that can be drawn are limited. For a better understanding of the basic mechanisms of sex differences, future studies should be designed with a primary focus on this topic. More specific data will help to determine the extent to which these differences will have implications for clinical management.

Acknowledgments

Dr. Soldin is partially supported by 5U10HD047890-03 NIH/NICHD Obstetrics Pharmacology Research Unit (OPRU) and by the Office of Research on Women's Health. Thanks to Dr. Anne Zajicek for reading the manuscript critically and for the helpful comments, and to Daniel O'Mara for his help in preparing the manuscript for publication.

Abbreviations

AAG	alpha-1 acid glycoprotein
AERS	Adverse Events Reporting System
ABC	ATP-binding cassette
BMR	basal metabolic rates
CO	Cardiac output

CYP3A	cytochrome P450-3A
FDA	Food and Drug Administration
GAO	General Accounting Office
GFR	glomerular filtration rate
GST	glutathione-S-transferase isoenzyme
HPA	hypothalamic-pituitary-adrenal
HPG	hypothalamic-pituitary-gonodal axis
IOM	Institute of Medicine
MDR1	multi drug resistance transporter-1 gene
NIH	National Institutes of Health
OATP	organic anion transporting polypeptide
PEPT1	H+/di tripeptide transporter
PGP	p–glycoprotein
SGAs	second-generation (atypical) antipsychotics
SSRI	selective serotonin reuptake inhibitors
UGT	Uridine diphosphate glucoronosyl transferase

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Table I

Anatomic differences between Men and Women

Parameter	Reference Adult Male	Reference Adult Female	Pregnant Female
Body Weight (kg) *	78	68	72.5
Body Length (cm) *	176	162	162
Body Surface Area (cm^2)	18,000	16,000	16,500
Total Body Water (L)	42.0	29.0	33.0
Extracellular Water (L)	18.2	11.6	15.0
Intracellular Water (L)	23.8	17.4	18.8

* CDC Advance Data No. 347 October 27, 2004

Table II

Reasons for Sex Differences in Adverse Event Reporting

Reason for sex difference	Pharmacological reason	Pharmacological factors
Women are more frequently overdosed	Pharmacokinetics	• Volume of distribution is smaller • Free fraction of drug is larger • Clearance from he body is slower
Women are more sensitive	Pharmacodynamics	• Alteration in receptor number • Alteration in receptor binding • Alteration in signal transduction pathway following receptor binding
Women take greater amount of medications	Drug interactions	• Alteration in pharmacokinetics (see row above) • Alteration in pharmacodynamics (see row above)

Table III

Physiological parameters which influence absorption

PARAMETER	PHYSIOLOGIC DIFFERENCE	PHARMACOKINETIC IMPACT
Gastric pH	acidity M >F> preg F	Altered absorption of acid/bases depending on specific drug ionization. In pregnancy decreased absorption of weak acid
Gastric Fluid Flow	M > F	Higher absorption in males
Intestinal Motility	M > F > pregnant F	Absorption increased in males
Gastric Emptying	M > F > pregnant F	Absorption, gastric hydrolysis increased
Dermal Hydration	Increased in pregnant F	Altered absorption in pregnant F
Dermal Thickness	M > F	Absorption decreased in males
Body Surface Area	M > pregnant F > F	Absorption increased when surface area larger
Skin Blood Flow	Increased in pregnant F	Absorption increased
Pulmonary Function *	M > pregnant F > F	Pulmonary exposure increased in males
Cardiac Output *	M > pregnant F > F	Absorption increased in males

* normalized for body surface area

Table IV

Pharmacokinetic parameters that exhibit sex differences for selected drugs

Drug	Pharmacokinetic Parameter	Male	Female	Comments
Theophylline	Non-smokers	9.3	6.0	The half-life of theophylline is shorter in women compared to men (either smokers or non- smokers), suggesting need for different schedule of administration.
	Smokers	6.9	4.6	
Acebutolol	Area under the concentration-time curve (ng*hr/ml)	4861	6410	The AUC profile is larger in women than men, suggesting greater therapeutic and potential side-effects.
Propranolol	Total Clearance	65.7	40.2	Propranolol is cleared more rapidly in men than women; this is also reflected in the higher clearance of the metabolites. Women have greater potential for therapeutic and adverse effects.
	Clearance (glucuronidation)	8.5	5.6	
	Clearance (side chain oxidation)	12.1	5.1	
Ethanol	Volume of distribution (L/kg)	0.62	0.45	First pass metabolism of ethanol is greater in men than in women. Also, the volume of distribution is smaller in women than men. These suggest the potential for greater blood concentrations among women than men.
	Clearance (mg/hr/kg)	78.6	88.6	
	First-pass metabolism (nmol/L*hr)	5.2	1.2	
Iron	Absorption measured as % of the dose incorporated into red blood cells	35.2%	45.0%	More ingested iron is absorbed by females than males

Table V

Sex Differences in Body composition parameters which influence distribution

PARAMETER	PHYSIOLOGIC DIFFERENCE	PHARMACOKINETIC IMPACT
Plasma Volume	pregnant F>M>F	Decreased concentration in pregnancy
Body Mass Index (BMI)	M>F	Higher in men
Average organ blood flow	Pregnant F>M>F	Higher in men
Total Body Water	M>pregnant F>F	Decreased concentration
Plasma Proteins	M, F>pregnant F	Free concentration increases in pregnancy
Body Fat	pregnant F>F>M	Increase body burden of lipid- soluble drug in women
Cardiac Output	M>pregnant F>F	Increase rate of distribution in men

Table VI

Sex Differences in plasma binding

Compound	Description
Testosterone	Plasma protein binding: F > M, Estrogen increases
Chlordiazepoxide	Plasma protein binding: M > F > Foc
Diazepam	Free fraction: Foc (1.99%) > F (1.67%) > M (1.46%)
Lidocaine	Free fraction: F (34%). M (32%) < Foc (37%)
Warfarin	Free fraction: F > M
Morphine, Phenytoin Oxazepam, Lorazepam	No differences

oc – oral contraceptives

Table VII

Sex differences in pharmacokinetics: biotransformation Physiological parameters which may influence differences in metabolism

PARAMETER	PHYSIOLOGIC DIFFERENCE	PHARMACOKINETIC IMPACT
Hepatic	higher basal metabolic rate (BMR) in M; hepatic metabolism in pregnant F	Increased metabolism
Extra-Hepatic	metabolism by fetus/placenta	Decreased metabolism
Plasma Proteins	free concentration increase in pregnant F	Increased metabolism

Weight for individuals of a given height will produce overlap in the BMR distributions for men and women.

TABLE VIII

Sex differences in hepatic clearance by route of metabolism/elimination

Phase I enzymes			
METABOLIC ROUTE	**Model Substrates**	**Drugs metabolized by route**	**Sex-Specific Activty**
CYP1A	Caffeine, nicotine paracetamol (acetaminophen)	Clomipramine, clozapine, olanzapine, paracetamol, tacrine, theophylline	**M>F**
CYP2C9	Dapsone, (*S*)-mephenytoin	Ibuprofen, (*S*)-warfarin, tolbutamide, fluvastatin, glipizide, losartan, irbesartan, piroxicam, tolbutamide, phenytoin, fluvastatin, nelfinavir	**M=F**
CYP2C19	(*S*)-Mephenytoin Diazepam	Lansoprazole, omeprazole, hexobarbital, mephobarbital, citalopram, celecoxib, irbesartan, imipramine, piroxicam, propranolol (in part)	**M=F**
CYP2D6	Dextromethorpha ndebrisoquine, sparteine	Codeine, encainide, flecainide, fluoxetine, hydrocodone, metoprolol, paroxetine, mexilitine, phenformin, propranolol, sertraline, timolol, haloperidol, clomipramine, desipramine, imipramine, propafenone, testosterone	**M<F**
CYP2E1	Chlorzoxazone	--	**M>F**
CYP3A	Midazolam, dapsone, cortisol, lidocaine, nifedipine, erythromycin, cortisol	Alprazolam, alfentanil, astemizole, atorvastatin, carbamazepine, cisapride, clarithromycin, cyclosporin, cyclophosphamide, diazepam, diltiazem, erythromycin, estradiol, fentanyl, indinavir, itraconazole, ketoconazole, lovastatin, quinidine, nimodipine, nisoldipine, quinidine, ritonavir, verapamil, tacrolimus, simvastatin, vincristine, vinblastine, tamoxifen, tirilazad, troglitazone	**M=F; F>M**
Phase II enzymes			
METABOLIC ROUTE	**Model Substrates**	**Drugs metabolized by route**	**Sex-Specific Activty**
UDP- glucuronosyl- transferases	Caffeine	Clofibric acid, diflusinal, ibuprofen, mycophenolate mofetil, paracetamol, zidovudine	**M>F**
Sulfo- transferases	Caffeine	--	**M>F**
N-Acetyl- transferases	Caffeine, dapsone	Catecholamine derivatives, mercaptopurine, isoniazid, hydralazine	**M=F**
Methyl- transferases	Norepinephrine, epinephrine	Ercaptopurine, azathioprine, dopamine, levodopa, 6-mercaptopurine, 6-thioguanine, tazathioprine	**M>F**

Table IX

Sex differences in pharmacokinetics: elimination Physiological parameters which may influence differences in excretion.

PARAMETER	PHYSIOLOGIC DIFFERENCE	PHARMACOKINETIC IMPACT
Renal Blood Flow GFR	pregnant F>M>F	Increase renal elimination
Pulmonary Function	M>pregnant F>F	Increase pulmonary elimination
Plasma Proteins	decrease in pregnant F	Decreased elimination

Table X

Some drugs that show Sex Differences in Pharmacokinetics*

Drug	Pharmacokinetic Parameter	Comments
Acebutolol	Area under the concentration-time curve	The concentration-time profile is larger in women than man, suggesting greater therapeutic and potential side effects.
Aspirin	Clearance, half-life	Aspirin is cleared more rapidly from women than men.
Benzylamine		Following transdermal absorption women excrete 3 times more than men
Beta-Blockers; metoprolol,	Oral clearance lower in women, lower volume of distribution in women resulting in higher systemic exposure	The greater reduction in blood pressure in women was due to pharmacokinetic not pharmacodynamic differences.
Cefazolin	Clearance, volume of distribution, half-life	**Clearance increases during pregnancy as a consequence half-life decreases. There is no change in volume of distribution during pregnancy**
Cefotaxime	Clearance	Clearance is decreased in women.
Ciprofloxacin	Clearance	Clearance is lower in women than men
IM Cephradine		Slower rate of absorption and lower bioavailability in the female
Clorazepate	Volume of Distribution, half-life	**Both V_d and $t_{1/2}$ are increased during pregnancy; initial concentration will be lower during but drug will persist longer in the body of women during pregnancy.**
Clozapine		significantly higher plasma levels for women
Diazepam	Plasma binding	Larger volume of distribution in women **Plasma binding decreases during pregnancy, as a result the free fraction will increase.**
Digoxin	Clearance	**Clearance increases during pregnancy, as a result more frequent administration may be needed.**
Erythromycin	Oral availability	**Oral availability decreases during pregnancy, as a result circulating concentrations are decreased**
Ethanol	Volume of distribution, Clearance, First-pass metabolism	When ethanol is ingested man metabolize more in first pass metabolism, in addition the volume of distribution is smaller in women.
Ferrous Sulfate	Absorption	Absorption higher in prepubertal girls than boys
Fluroquinolones	Volume of distribution	Lower in women
Gemcitabine	Clearance	Clearance is lower in women than men.
Heparin	Clearance	Clearance is lower in women than men.
Iron	Absorption measured as % of the dose incorporated into red blood cells	More ingested iron is absorbed by women than men
Lithium	Clearance	**Clearance is increased during pregnancy**
Mefloquine	Clearance, half-life	**Clearance is increased during pregnancy**
Methylprednisolone	Plasma binding, clearance, volume of distribution, half-life	Plasma binding and V_d are similar in men and women. CL is increased in women and as a consequence half-life is shorter.

Clin Pharmacokinet. Author manuscript; available in PMC 2013 May 05.

Drug	Pharmacokinetic Parameter	Comments
Metronidazole	Volume of distribution	Smaller volume of distribution and increased clearance resulting lower AUC in women
Metoprolol	Plasma binding, clearance, volume of distribution, half-life	**Oral availability decreases during pregnancy.** Clearance increases during pregnancy, but is smaller in women than men. Vd smaller and women than men, but increases during pregnancy. Plasma binding is unaffected by Sex or pregnancy.
Midazolam	Considered to be probe for CYP3A4, not substrate for PGP	No sex difference in clearance following either oral or intramuscular administration. Interpretation complicated by **differences in intestinal and hepatic CYP3A4 levels**
Mizolastin	Oral availability	Longer duration for absorption in men, contributing to variability in drug concentrations in men and women
Naratriptan	Oral availability, peak concentration	Oral availability is greater and women than busy man, as result's peak concentration is higher in women than men.
Ofloxacin	Clearance	Clearance is lower in women than men
Olanzapine	Higher activity in women for CYP3A4 and CYP2D6	significantly higher plasma levels for women
Ondansetron	Oral availability, clearance	Oral availability is increased in women.
Phenobarbital	Plasma binding, clearance	**Plasma binding is unchanged, clearance is increased during pregnancy.**
Phenytoin	Plasma binding	**Plasma binding decreases during pregnancy.** However, the intrinsic clearance is unchanged so the free concentration is unchanged.
Prazosin	Clearance, half-life	**Clearance decreases during pregnancy.**
Prednisolone	Distribution	Oral clearance and volume of distribution significantly higher in men
Propranolol	Plasma binding, clearance, volume of distribution, half- life	Plasma binding is similar among men and women; however plasma binding increases during pregnancy. Clearance is smaller in women than men. V_d is similar in both men and women and does not appear to be altered during pregnancy. Half-life is decreased in women compared to man but does not appear to be altered during pregnancy.
Propranolol	Clearance	Propranolol is cleared more rapidly in men; this is also reflected in the higher clearance of metabolites. Therefore, women have greater potential for therapeutic and adverse effects.
Quinidine	Plasma binding,	**Plasma binding decreases during pregnancy.**
Quinine	Plasma binding, clearance, volume of distribution, half- life	Plasma binding is unaltered during pregnancy, as is clearance. Vd decreases during pregnancy, as does half-life.
Rifampicin	Women absorb the drug more efficiently	
Rizatriptan	Urinary excretion, clearance, volume of distribution, half- life	Urinary excretion is similar in men and women. Clearance is greater in men.
Rocuronium	Distribution	Prolonged drug duration due to higher fat content and lower organ blood flow in women
Salicylate	Absorption	Increased rates of absorption in women than men
Selective Serotonin Reuptake Inhibitors	Plasma concentrations are higher in women than man	Decreased metabolism by hepatic CYP
Sulfasoxazole	Plasma binding	**Plasma binding decreases during pregnancy.**

Drug	Pharmacokinetic Parameter	Comments
Theophylline	Plasma binding, clearance, volume of distribution,	**Plasma binding decreases during pregnancy. Vd increases as expected from protein binding and changes in physiological spaces. Decreased hepatic clearance is offset by increased renal clearance.**
Valproic acid	Plasma binding	**Plasma binding decreases during pregnancy.**
Vecuronium	Distribution	Prolonged drug duration due to higher fat content and lower organ blood flow in women
Verapamil; Calcium channel blocker	Clearance following intravenous administration more rapid in women, but oral clearance higher in man than women. Substrate for both CYP3A4 and PGP.	Sex-differences in hepatic and gut CYP3A4 and PGP lead to complex differences in clearance between man and women. Bioavailability from the gut is greater in women than in man. The greater bioavailability leads to increased systemic exposure in women.
	Oral clearance is lower in women than [38, 39]	

* Pregnancy-related PK changes are in bold font