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SEX DIFFERENCES IN PHARMACOKINETICS AND PHARMACODYNAMICS

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■ **Abstract** The importance of reviewing and studying sex-based differences in pharmacologic parameters is demonstrated by the increasing data on gender variation in drug efficacy and toxicity profiles. Sex-based differences in the four major factors that contribute to interindividual pharmacokinetic variability—bioavailability, distribution, metabolism, and elimination—are theorized to stem from variations between men and women in factors such as body weight, plasma volume, gastric emptying time, plasma protein levels, cytochrome P450 activity, drug transporter function, and excretion activity. Sex-determined variations in pharmacodynamics have traditionally been more difficult to study, but a number of recent studies have explored these differences. This review examines the biologic basis of differences in pharmacokinetics and pharmacodynamics between the sexes and summarizes studies that have addressed these differences. As an example, sex-based variation in the efficacy and toxicity of antiretroviral therapy in human immunodeficiency virus (HIV)-infected patients is explored more thoroughly to illustrate some of the factors underlying sex-based differences in drug therapy.

INTRODUCTION

In 1999, the National Institutes of Health (NIH) published a six-volume report entitled the *Agenda for Research on Women's Health for the 21st Century*, which, among other dictums, claimed that because "gaps in knowledge remain regarding the behavior of drugs in women . . . [and] over-reliance on traditional male-oriented medical practices may ill serve women . . . gender-related pharmacokinetic and pharmacodynamic differences" (1) must necessarily be assessed. Although the Food and Drug Administration (FDA) mandated in 1998 that new drug applications

must include data on safety and effectiveness by sex, a 2001 U.S. General Accounting Office (GAO) investigation revealed that over one-third of the FDA-approved drugs in the preceding two years failed to provide such gender-specific information (2). Although women may be increasingly represented in clinical trials for new medications, failure to analyze sex-related differences in pharmacokinetics, side-effect profiles, and efficacy of these medications limit the generalizability of such data to women. This review explores the biologic and molecular basis for sex-related disparities in pharmacokinetics and pharmacodynamics, describes existing examples of sex-based differences in drug effects and safety, and makes recommendations for future pharmacological research.

PHARMACOKINETICS

Pharmacokinetics is the study of the relationship between drug dosage and concentration of drug over time in blood or plasma, or, preferably, in cells and tissues, which may be more representative of the site(s) of action. Pharmacodynamics relates pharmacokinetic parameters to pharmacological effect. Much of the available literature explores sex-based differences in pharmacokinetics of drugs, rather than differences in pharmacodynamics or clinical effects. However, increasing data is accumulating on disparate clinical outcomes by sex for various therapies, with or without defined pharmacokinetic differences. Sex-based differences in the four major factors that contribute to interindividual pharmacokinetic variability—bioavailability, distribution, metabolism, and elimination—are explored in greater depth below. Studies that reveal pharmacokinetic variability for drugs based on sex attributable to one or more of these four factors are presented. Table 1 summarizes the various factors that contribute to each pharmacokinetic variable and sex differences that have been identified for these factors.

Bioavailability

The bioavailability of a drug is assessed by the rate and extent of oral absorption. Factors that influence drug absorption include gastric acid secretion, gastric emptying time, gastrointestinal (GI) blood flow, and surface area (3), along with the effects of presystemic hepatic and gut metabolism and transport. Some of these factors have been investigated for disparities by sex. Gastric acid secretion and characteristics of stomach and proximal jejunal fluids, including pH, osmolality, electrolyte concentrations, and levels of bile acids and proteins, do not seem to vary significantly by gender in controlled experiments (4–7), although conflicting reports exist (8). However, GI motility is influenced by sex hormones (9, 10), implying that sex-based differences in motility may exist and that transit times in women may vary throughout pregnancy and the menstrual cycle. Estrogen and its equivalents may inhibit gastric emptying (11, 12), whereas the effects of progesterone vary depending on concentration: Low concentrations increase gastric emptying in rats and high concentrations inhibit emptying (13, 14). Gastric transit

TABLE 1 Sex differences in pharmacokinetic parameters

PK parameter	Components	Sex-based differences
Bioavailability	Passive component: gastrointestinal tract physiology.	Gastric emptying time is slower in females than males, mainly secondary to the effects of estrogen.
	Active component: extrusion by drug transporters, such as intestinal p-gp.	Intestinal p-gp levels do not consistently seem to vary by sex.
	Gut metabolism: gut enzymes, such as alcohol dehydrogenase and intestinal CYP3A4.	Gastric levels of alcohol dehydrogenase are higher in males than females; intestinal CYP3A4 levels do not consistently vary by sex
Distribution	Body composition: body mass index, percent body fat, plasma volume, and organ blood flow.	Women have lower body weights and lower BMI than men; women have 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.
	Protein binding: extent of tissue and protein binding of the drug.	Albumin concentrations do not seem to consistently vary by sex, but endogenous estrogens decrease levels of AAG in the plasma, so women have lower concentrations of AAG than men. Exogenous estrogens increase levels of the serum-binding globulins (such as sex-hormone binding globulins, corticosteroid-binding globulin, and thyroxine-binding globulin).
Metabolism	Hepatic enzymes: Phase I metabolism reactions in the liver include oxidation, reduction, and hydrolysis and are mediated through the cytochrome P450 system.	Data on varying levels of CYP expression and activity using in vitro systems exist, but the majority of studies that examine CYP (mainly CYP3A4) substrates for differences in pharmacokinetic parameters in men and women are inconsistent; general trend toward higher rates of metabolism for CYP3A4 substrates in women versus men.
	Hepatic transporters: hepatic p-gp or MDR1.	Men seem to have higher hepatic p-gp levels than women, with higher rates of drug clearance in women versus men for drugs that are substrates of p-gp.
Excretion	Renal clearance: renal excretion is dependent on filtration, secretion, and reabsorption.	Renal clearance of drugs that are not actively secreted or reabsorbed is dependent on GFR, which is directly proportional to weight; sex differences for these drugs are attributable to weight differences. Drugs that are actively secreted by the kidney may show sex differences in excretion.

time has clearly been demonstrated to be slower in females than males (15–19). Changes in gastric emptying time have been observed in pregnancy (10), but not consistently during the menstrual cycle (20, 21).

GI enzymes responsible for drug metabolism also vary by sex. For example, gastric alcohol dehydrogenase activity is higher in males than in females in both humans (17, 22, 23) and animals (24, 25), resulting in higher blood concentrations of ethanol in females compared to males following an equivalent ingestion. Enterocytes also express significant levels of isoenzymes of cytochrome P450 3A (CYP3A), which contribute significantly to the first-pass metabolism of some orally administered drugs. Significant differences in gut expression of CYP3A enzymes, however, between male and females have not been consistently observed (26, 27). Variability in intestinal expression of enzymes that modulate gut transport of drugs, such as p-glycoprotein (or multidrug resistance transporter-1, MDR-1), may result in sex-based variability in plasma drug concentrations. Although pharmacogenomic studies reveal that polymorphisms of the human MDR-1 gene have been shown to group by race (28, 29), gender-specific variation in expression of intestinal p-glycoprotein has not been demonstrated.

Several clinical pharmacokinetic studies reveal differences in drug absorption and bioavailability for certain drugs based on gender. For example, orally administered verapamil is cleared faster in men than women, a difference that is not observed after intravenous (IV) administration of this drug (30), suggesting that intestinal processes modulate sex-specific differences in verapamil pharmacokinetics (30). A population pharmacokinetic analysis of mizolastine, an orally administered antihistamine, demonstrated a longer duration for absorption of this drug in men versus women, contributing to variability in drug concentrations by gender (31). Ferrous sulfate absorption, measured with the aid of radioisotope labeling, was found to be higher in prepubertal girls than boys (32), suggesting that hormonal differences may contribute to sex-based pharmacokinetic variability for this medication. Two studies have demonstrated an increased rate of absorption for some salicylate formulations in females compared to males (33, 34), although another fails to show this disparity (35).

In summary, although gastrointestinal motility and metabolizing enzymes vary by sex, studies have not consistently shown a difference in drug bioavailability between men and women. Furthermore, studies that examine differences in bioavailability are generally few and confounded by variability in other pharmacokinetic factors, such as distribution, metabolism, and excretion. The present evidence, however, suggests that sex-based differences in bioavailability are not of great clinical significance.

Distribution

The distribution of a drug is affected by 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. Women have a higher body fat

percentage, a lower average body weight, a smaller average plasma volume, and lower average organ blood flow than men, with obvious implications for disparities in the rate and extent of drug distribution. Moreover, the major protein groups responsible for binding drugs in human plasma are influenced by concentrations of sex hormones, so that plasma drug binding can clearly be influenced by gender. As many of the factors that affect the volume of distribution for a drug (defined as the ratio of the plasma concentration to the amount of drug in the body) differ by sex, differences in drug distribution may be a component of sex-based differences in pharmacokinetics of various compounds.

Owing to differences in body fat percentage, lipophilic agents may have a relatively greater volume of distribution and water-soluble compounds may exhibit a relatively lower volume of distribution in females compared to males. Increased fat stores and differences in organ blood flow in women versus men have been implicated in the faster onset of action and prolonged duration of neuromuscular blockade in females with lipophilic paralyzing agents, such as vecuronium (36–39) and rocuronium (40). A larger volume of distribution for diazepam has been observed in females versus males (41, 42), with differences in both body fat proportion and sex-dependent changes in protein binding being cited for this disparity. The water-soluble compound, metronidazole, demonstrates a smaller volume of distribution in women versus men, although increased clearance of metronidazole in females versus males accounts for a lower area-under-the-concentration-time curve (AUC) for this drug in females (43). A smaller volume of distribution for the water-soluble fluoroquinolones in women versus men (44, 45) can be normalized for ofloxacin by adjusting for gender-related differences in body weight (44). Both the oral clearance of prednisolone and the volume of distribution of this compound are significantly higher in men compared with women (46).

In addition to the physical differences between men and women, which lead to disparities in drug distribution, differences in plasma protein binding by sex can theoretically lead to differences in pharmacokinetic parameters for certain agents. Albumin, alpha-1 acid glycoprotein (AAG) and alpha-globulins are the main binding proteins for various drugs in plasma. Albumin concentrations do not consistently vary by sex, but AAG levels and states of AAG-glycosylation vary in association with endogenous and exogenous estrogens (47–50), which both decrease levels of AAG in the plasma and induce hepatic glycosylation of these proteins (50). In addition, exogenous estrogens increase levels of the serum-binding globulins, which include sex-hormone binding globulins, corticosteroid-binding globulin, and thyroxine-binding globulin (51).

During pregnancy, the effects on binding proteins are complex. As pregnancy progresses, the concentration of albumin, along with other plasma proteins, decreases (52). However, the effects of pregnancy on the concentration of AAG is under debate: Two studies report an overall decrease in AAG concentration over the course of pregnancy (53, 54), one study reports no change (55), and another reports decreases in AAG levels throughout pregnancy (52). Compounding the inconsistent data regarding concentrations of serum proteins, unresolved questions

still exist regarding drug protein binding capacity in the setting of pregnancy. Some researchers report that there is a steady increase in the production of endogenous ligands, such as free fatty acids, during pregnancy that compete for drug binding sites distinct from their own on albumin (56, 57). Furthermore, protein-binding capacity may be reduced secondary to intrinsic alterations in protein structure during pregnancy (58).

Variations in levels of plasma binding proteins can alter the free fraction of drugs. The free fraction is the active form of the drug. Therefore, it may be necessary to modify the interpretation of total drug concentrations during therapeutic drug monitoring or in the context of a pharmacokinetic study. Although sex-based differences in binding may lead to differential pharmacokinetics for some compounds by sex, major studies that explore this phenomenon in humans are lacking. One study in sheep showed that male animals had a significantly lower binding of albendazole metabolites to globulins and albumin when compared to female animals (59), thought to be secondary to sex-dependent variation of plasma-binding molecules. Another study showed differential effects of morphine on the induction of corticosteroid-binding globulin in male rats versus female rats (60). Therefore, although the gender-based difference in plasma protein binding is postulated as a theoretical contributor to sex-dependent pharmacokinetics, the extent of this contribution has not yet been precisely defined in humans.

Metabolism

Sex-based differences in drug metabolism seem to play a greater role in intergender pharmacokinetic variability than any of the other pharmacokinetic parameters. Hepatic clearance of drugs is a function of liver blood flow and hepatic enzyme activity. Although cardiac output and hepatic blood flow are lower in women than men, gender differences in hepatic enzymes seem to play the major role in determining pharmacokinetic variability by sex. Hepatic drug metabolism is divided into two, usually sequential, enzymatic reactions: 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. Important sex differences in some of the key cytochrome P450 enzymes have been demonstrated by some of the studies summarized below.

The cytochrome P450 3A (CYP3A) subfamily is responsible for the initial hepatic metabolism of a large number of medications in current clinical use, with CYP3A4 representing the predominant member of the subfamily in humans. Other prominent cytochrome P450 enzymes include CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP2E1. Furthermore, drug metabolism can be mediated through both intestinal CYP enzymes and their hepatic counterparts (61). The frequency of variant alleles for the hepatic metabolizing enzymes has been shown to differ among ethnic groups (62). These enzymes have also been shown to vary by sex in both humans and animals. Multiple pharmacokinetic analyses reveal

sex-based differences in drug concentrations that are attributed to gender differences in hepatic enzyme expression. These differences are influenced by endogenous sex hormone production (63), as well as hormonal changes associated with oral contraceptive use, pregnancy, and menopause.

Sex-based disparities in cytochrome P450-mediated drug metabolism have been examined through a variety of methods, including (*a*) the demonstration of a sex-based differential in mRNA expression for various CYP enzymes in peripheral leukocytes (despite the uncertain clinical significance of that finding) and within hepatocytes, (*b*) the direct examination of variability in CYP activity by sex, or (*c*) the demonstration of sex-based variability in pharmacokinetic parameters of drugs metabolized by these enzymes. The following examples summarize some of the seminal studies that attempt to demonstrate sex-based variance in drug metabolism.

IN VITRO DATA In studies performed in humans, one group showed that the expression of CYP1B1 mRNA levels in peripheral leukocytes was significantly higher in women than in men (64), a finding of uncertain clinical significance because drug metabolism does not occur in leukocytes and CYP1B1 does not clearly contribute to the metabolism of any drugs in humans. Another group looked at 10 male and 10 female human liver microsomal preparations and evaluated the contents and activities of specific hepatic enzymes, including CYP3A4 (65). Female livers had a significantly higher mean content of CYP3A4 and female liver microsomes exhibited a higher rate of the CYP3A4-mediated ifosfamide N-dechloroethylation reaction than in vitro microsome preparations from males. Erythromycin is metabolized through CYP3A-mediated *N*-demethylation, and in vitro studies have used microsomes prepared from human livers to compare CYP3A4 activity in males versus females (66). One study showed that CYP3A4 activity is 24% higher in women than men (66), a finding that was consistent with other studies on microsomes from hamster livers (67).

In contrast are studies that fail to show sex-based variability in CYP levels or activity in humans when examined in either in vitro or in vivo systems. One study used an in vitro human liver microsome system and demonstrated that the mean amounts and activity of cytochrome P450-microsomal monooxygenases do not differ by sex (68). Another group used the liver microsome system to investigate a variety of cytochrome P450 enzymes and found no clear sex-related differences in P-450 levels or metabolizing activity, with the exception that CYP1A2 activity was higher in Caucasian women than men (69). A third study used the microsome system to evaluate the content of cytochrome P450 proteins in human livers and found that gender did not influence the expression of any of the CYP proteins (70). As a cautionary note to interpreting these studies, the in vitro liver microsome assay lacks the systemic hormonal milieu of the male or female body, which may lead to disparate results from in vivo analyses.

Sex-based variance in cytochrome P450 levels in animal models has also been examined. Various cytochrome P450 enzymes in rats, including CYP3A9 (71) and CYP4Fs (72), show higher levels of both mRNA and protein expression in the

livers of females versus male livers, with upregulation of such enzymes induced by endogenous and exogenous estrogens. Male-specific hepatic cytochrome isoenzymes, such as CYP2C11 and CYP3A2, can be induced in female rat livers with the administration of oxandrolone, a synthetic androgen steroid hormone (73). Upregulation of mRNA expression of the female-predominant murine CYP enzymes, CYP3A44 and CYP3A41, is modulated by estradiol levels in mice (74). The administration of dexamethasone (75), phenobarbital (76), and clofibrate (77) in rats has differential effects on the induction of CYP3A isoenzymes by sex. Finally, a study using microsomes from the livers of minipigs and pigs to measure the in vitro activity of various cytochrome P450 enzyme systems showed that the activities of both CYP1A2 and CYP2E1 were four times higher in female than male minipigs and two times higher in female than male pigs (78).

IN VIVO DATA Sex-based differences in pharmacokinetic parameters of drugs metabolized by the cytochrome P450 system are manifestations of probable variance in CYP content or activity by sex. For instance, erythromycin is a well-studied substrate of CYP3A4 and its metabolism has been examined for sex differences. One group showed that erythromycin is cleared more rapidly after IV dosing in women versus men (79), which is thought to be a hepatic CYP3A4-mediated effect. The erythromycin breath test has been validated as an in vivo assessment of CYP3A4 activity (80, 81) and several studies have demonstrated greater CYP3A4 activity in women versus men using this test (82, 83).

Another classic substrate of CYP3A4 is midazolam, a benzodiazepine that has been extensively evaluated as a probe for human CYP3A4 activity (84, 85). The majority of the studies evaluating sex differences in CYP3A4 activity using midazolam do not reveal any significant differences in intravenous or oral midazolam metabolism by gender (86–91), although a few investigators have shown greater clearance of the drug in women compared to men (92, 93). Overall, the weight of the evidence that has probed hepatic CYP3A activity using intravenous midazolam has failed to show a significant sex-related disparity. Intestinal CYP3A4 levels may be higher in women than men (94–96), but the clinical significance of this difference is unclear, as studies examining oral midazolam metabolism do not show a consistent sex-related difference.

Another drug that has been relatively well studied as a probe for CYP3A4 activity is verapamil, one of the nondihydropyridine calcium channel blockers. Orally administered verapamil clears more quickly in men than women (97), which is thought to be a multifactorial phenomenon, including variations in hepatic metabolism. Furthermore, higher absolute bioavailability of this compound in women may translate to greater pharmacodynamic effects on blood pressure and heart rate in the latter group (97). A subsequent study by the same investigators in seven men and six women found that oral clearance was 43 ± 15 mL/min/kg in women compared with 75 ± 29 mL/min/kg in men after administration of sustained-release verapamil and 35 ± 16 mL/min/kg in women compared with 65 ± 31 in men after administration of regular-release verapamil ($P < 0.05$).

A recent report by the same group verified this disparity in oral clearance of verapamil by studying the largest group of individuals to date (135 men and 51 women) on sustained-release oral verapamil (98). Apparent oral clearance of sustained-release verapamil in this report was 23.8 $\pm$ 2.3 mL/min/kg in women compared with 18.6 $\pm$ 3.4 mL/min/kg in men. Pharmacodynamic differences in drug response by sex were not reported in this analysis. Hepatic metabolism of verapamil by the CYP3A4 system has been shown to be greater in women versus men, resulting in a clearance of intravenous verapamil of 13.7 $\pm$ 4.3 ml/min/kg (mean $\pm$ SD) in women compared to 12.6 $\pm$ 3.4 ml/min/kg in men ($p = 0.076$) in a group of 42 men and 42 women (97). In contrast, other studies have shown no differences in clearance of oral verapamil between men and women (99, 100), although these studies both had a total sample size of only 12 participants each.

Overall, the weight of the evidence shows negligible sex differences in midazolam pharmacokinetics, whereas the data on verapamil kinetics more consistently reveals higher clearance of the drug in women compared to men. These conflicting data have led some authors to conclude that CYP3A4 metabolism (both intestinal and hepatic) may vary by sex, but other pharmacokinetic factors (e.g., absorption, binding, volume of distribution) for these compounds may lead to the varying results in men and women. One group has presented an alternative hypothesis involving the transporter p-glycoprotein (p-gp) to explain the inconsistency in gender-based pharmacokinetic differences with CYP3A4 substrates (101), as described below.

The multidrug efflux transporter p-gp is membrane bound, and efflux of a compound by p-gp will effectively lower the intracellular concentrations of a drug. Drugs that encounter hepatocytes from the bloodstream need to cross the cell membrane to become intracellular for interaction with CYP3A4. Men may have higher hepatic p-gp levels than women (102), leading to higher intracellular hepatic drug concentrations in women with subsequent increases in CYP3A4 metabolism and clearance of some drugs in this group. Midazolam is a substrate of CYP3A4, but not of p-gp, whereas verapamil is a substrate of both. The authors thus explain the sex-based disparity in verapamil versus midazolam pharmacokinetics as a consequence of the former drug's interaction with hepatic and/or intestinal p-gp (101). A literature survey to determine whether p-gp levels contribute to sex-related differences in the clearance of CYP3A4 substrates reveals a general concordance between the predicted higher drug clearances in women compared with men for drugs that are substrates of both p-gp and CYP3A4 (101). However, most of the studies that examined drugs that are substrates of CYP3A4, but not p-gp, demonstrated no significant sex-based pharmacokinetic differences. Other groups have similarly suggested that sex-related differences in p-gp expression may be responsible for clearance disparities in CYP3A4 substrates (103). Other reports have investigated the pharmacokinetic and clinical significance of gender differences in a variety of membrane transporters (104).

Although the majority of the studies that have been performed to evaluate sex-based differences in CYP activity have focused on CYP3A4, other cytochrome

P450 enzymes have been examined for sex differences in activity as well. For instance, the CYP2D6 enzyme has been shown to be important in the metabolism of a number of antipsychotic agents (105). One study showed that tardive dyskinesia as a side effect of various antipsychotic agents develops more frequently in female Chinese schizophrenic patients than in males secondary to the increased frequency of a defective CYP2D6 allele in Chinese women (106). In addition, both expression and functional studies suggest that CYP1A2 activity, which has been typically probed by the quantification of caffeine metabolism (107) and is a prominent enzyme in the metabolism of antipsychotics (105), is higher in females than in males (69, 70). One group used the drug probes mephenytoin and omeprazole to evaluate for gender differences in CYP2C19 activity (108). No differences in CYP2C19 activity were observed between women not taking oral contraceptives and men with either the mephenytoin probe ($P = 0.48$) or the omeprazole probe ($P = 0.77$); oral contraceptives, however, were found to significantly inhibit CYP2C19 activity. Table 2 summarizes the general trends of sex-based activity differences among the prominent cytochrome P450 enzymes in humans.

STUDIES OF PHARMACOKINETIC PARAMETERS IN FEMALES DURING HORMONAL FLUCTUATIONS Based on the theory that sex hormones play the dominant role in modulating sex-based differences in pharmacokinetics, several studies have examined pharmacokinetic variation through hormonal fluctuations to bolster evidence for sex-based differences in pharmacokinetics. These studies have yielded conflicting results, as illustrated by the following examples.

One of the groups that investigated the clearance of midazolam between the sexes (86) as described above also looked at intrasubject differences in midazolam clearance throughout the phases of the menstrual cycle. This report found no significant differences in midazolam clearance in the same woman through different phases of the menstrual cycle. Another group also used midazolam clearance as a probe of CYP3A4 metabolic activity throughout the menstrual cycle and tested for variability in midazolam plasma disposition (109). Intravenous midazolam was administered to female participants with normal menstrual cycles on three separate occasions during the same cycle, specifically days 2 (menstrual phase),

TABLE 2 Sex differences in cytochrome P450 activity

Metabolizing enzyme	F > M	F = M	F < M	References
CYP3A4[a]	•			65–70, 79, 82, 83, 86–93, 97–100
CYP2C19		•		108
CYP2D6			•	106
CYP1A2			•	69, 70

[a]See text, as conflicting studies for activity of CYP3A4 exist.

13 (estradiol peak), and 21 (progesterone peak). Midazolam plasma concentrations did not differ between phases, indicating that menstrual cycle variability in the metabolism of CYP3A4 substrates may not be significant.

Another study examined the role of the menstrual cycle in plasma disposition of the migraine agent, eletriptan (110). Pharmacokinetics were evaluated during each of four menstrual cycle phases: (*a*) menses, days 1 to 4; (*b*) follicular, days 6 to 10; (*c*) ovulatory, days 11 to 13; and (*d*) luteal, days 21 to 24. No significant differences in eletriptan disposition were found between the four phases. In another study, CYP3A4 and CYP2D6 activities were estimated by administration of dextromorphan and measurement of urinary dextromorphan metabolites in a group of men and women, with menstrual phases recorded in the females (111). The authors observed no impact of sex or menstrual cycle phase on isoenzyme activity, although the high intrasubject variability in dextromorphan urinary metabolites could have limited the sensitivity of this method.

In terms of differences in pharmacokinetics related to menopause, premenopausal women had higher rates of midazolam clearance than postmenopausal women in one study, but the effects of menopause on CYP3A4 activity were not reversed by hormone replacement (112). Another group looked at both intravenous and oral midazolam clearance in 12 young women (27 ± 5 years), 10 elderly women receiving estrogen replacement therapy (HRT) (71 ± 6 years), and 14 elderly women not receiving HRT (71 ± 5 years) and found no significant differences in systemic or oral clearance among the three groups (113), arguing that menopause and HRT do not alter intestinal or hepatic CYP3A4 activity. Another study found no significant differences in the clearance of IV erythromycin in groups of women who were premenopausal, postmenopausal and not on HRT, postmenopausal on estrogen replacement therapy, and postmenopausal on estrogen and progesterone replacement therapy (114).

Despite the studies above that show no significant differences in drug metabolism by menopausal status, other studies demonstrate that the changes in sex hormone profiles between menstruating and postmenopausal women do affect the pharmacokinetics of some agents. The same study that found no significant differences in the clearance of IV erythromycin by menopausal or HRT status demonstrated significant differences in prednisolone pharmacokinetics by state of menopause (114): The unbound clearance of prednisolone was significantly lower in postmenopausal women (11.6 ± 2.3 ml/min/kg) than in premenopausal women (16.6 ± 3.5 ml/min/kg), although HRT did not affect the pharmacokinetics of prednisolone. Another report examined the pharmacokinetics of alfentanil, an anesthetic agent and CYP3A4 substrate, and found that plasma alfentanil clearance was increased in females over 50 years of age compared to females less than 50; a similar pharmacokinetic difference by age was not observed in men (115). Another group performed a reanalysis of these data and found that 67.5% of the variation in alfentanil clearance in women was explained when clearance values were divided into groups by menopausal status (116). One study demonstrated a consistently higher clearance of tirilazad, an antioxidant used in the treatment of acute ischemic

or traumatic central nervous system injury, in premenopausal women than in postmenopausal women, which seems to be linked to CYP3A4 activity; this effect was not reversed by HRT (112). Overall, therefore, conflicting data exist on whether menopausal status or the estrogen and progesterone levels in HRT significantly affect drug metabolism in women.

Excretion

Drug excretion is usually mediated by the kidney or the liver, with the vast majority of drugs following first-order kinetics. Renal clearance of drugs that are not actively secreted or reabsorbed is dependent on the glomerular filtration rate (GFR), which is directly proportional to weight and consequently higher on average in men than women. Hence, sex differences in rates of renal excretion for most drugs are most likely attributable to simple weight differences (117–119).

Drugs that are actively secreted by the kidney may show sex differences in excretion, however. A recent study looked at the influence of sex on the pharmacokinetics of para-aminohippuric acid (PAH), the reference substance for the renal organic anion transport systems, and furosemide, a substrate for this transport system, in rats (120). Female rats displayed a lower PAH and furosemide systemic clearance and a lower excretion rate for both drugs, presumably secondary to sex-based differences in renal secretion (121). Sex hormone differences between males and females seem to be responsible for disparities in renal secretion for organic anions in rats (122–124). One study in humans has shown increased renal clearance of amantadine, an organic cation requiring secretion by the kidneys (125), in men compared to women. Further study on sex-based differences in renal excretion in humans is required to clearly delineate the contribution of this factor.

PHARMACODYNAMICS

Pharmacodynamic disparities in drug response based on sex have not been studied as extensively as pharmacokinetic differences, partially because pharmacologic effects can be difficult to quantify. Sex-related effects on pharmacodynamics are distinguished from differences in pharmacokinetics by demonstrating that the same plasma concentration of a drug in the two sexes does not yield the same pharmacologic outcome. Some examples of studies that have examined pharmacodynamic differences between men and women are summarized below.

One study cited earlier showed that the oral clearance and the apparent volume of distribution of prednisolone were both higher in men than women, but that these pharmacokinetic differences were not accompanied by sex-based pharmacodynamic differences (46). Specifically, the 50% inhibitory concentration (IC50) values for effects of prednisolone on cortisol secretion and T-helper lymphocyte or neutrophil trafficking were not statistically different between men and women in this study (46). However, another group found a significantly smaller IC50 value in women (0.1 versus 1.7 ng/ml) for methylprednisolone suppression of cortisol

secretion, indicating increased sensitivity (126). Sex-based differences in the pharmacodynamics of prednisolone may be mediated by endogenous estrogens; for instance, the IC50 values for effects of methylprednisolone on basophil trafficking are related to estradiol concentrations in a log-linear fashion in women, with increased sensitivity found at higher estradiol concentrations (126).

In the study cited earlier that demonstrated increased bioavailability and decreased clearance of oral verapamil in women compared to men (97), differences in pharmacologic effect secondary to these sex-based pharmacokinetic differences were observed, with greater reductions in blood pressure and heart rate observed in women compared to men taking oral verapamil. Another study that examined sex-based pharmacokinetic differences for oral verapamil showed that the reduction in mean arterial blood pressure owing to the drug was closely correlated with its plasma concentration, although without any interaction by sex (127).

Sex differences in response to various analgesics have been fairly well studied (128), mainly because men and women seem to respond differently to the syndrome of pain (129–132). Opioid analgesics seem to have different pharmacodynamic responses in 60% of studies comparing male to female animals, with directionality depending on the type of animal studied and the predominant opioid receptor involved (μ, κ, or δ) (133). The majority of the studies in humans point to greater analgesic effects with opioid agonists in females compared with males (128, 134–136). Furthermore, women may have more side effects than men when taking opioid agonists. A recent study demonstrated that women had a 60% higher risk of nausea and vomiting than men with the use of opiates, although efficacy did not differ between the two groups (136a).

Sex differences in analgesic response have also been observed with nicotine and other cholinergic agents, although the majority of the studies have been performed in animals, with directionality of the gender disparity dependent on the species of animal and type of drug (137, 138). Studies involving these agents have been rare in humans, but one group did investigate the analgesic effects of a nicotine patch in men and women (139). Ratings of electrocutaneous stimulation were obtained 2.5 hours after patch application from 30 male and 44 female smokers and nonsmokers on either placebo or a nicotine patch (7–21 mg/24 h transdermal). Nicotine increased the pain threshold and tolerance ratings of men, but had no effect on the pain ratings of women. Furthermore, there was no effect of smoking history on pain ratings among men, suggesting that the changes in pain perception reflect a direct inhibition of pain by nicotine rather than relief from nicotine withdrawal symptoms.

The sexual dimorphism of nociceptive systems is probably attributable to sex steroid differences; animal studies reveal sex differences in endogenous opioid and corticosteroid release (140, 141), as well as gender differences in neurochemical receptor concentration regulation in the brain (140, 142). Sex differences in pharmacologic response to analgesics are presumably mediated by pharmacodynamic differences, including sex differences in drug-receptor affinity, receptor density, or signal transduction pathways (128).

Another group of agents that have been investigated for sex-based differences in pharmacodynamics are the anesthetic agents (143). Females have 20%–30% greater sensitivity to the muscle relaxant effects of vecuronium (144), pancuronium, and rocuronium (40) compared to men. However, the differences may be attributable to the lower volume of distribution of these drugs in females rather than pharmacodynamic effects. On the other hand, pharmacodynamic differences seem to explain a 30%–40% increase in sensitivity to the effects of propofol in males compared to females (145–147). Diazepam impairs psychomotor skills to a greater extent in women compared to men (148), which may be explained by an increased pharmacodynamic sensitivity to this compound in women.

Many psychotropic medications also appear to exhibit sex-mediated differences in pharmacodynamics (149–151). Women show greater improvement in psychotic symptoms and more severe adverse side effects with typical antipsychotic agents than do men (152, 153), although detailed studies as to whether these differences are mediated through pharmacokinetic or pharmacodynamic mechanisms are needed (149). Furthermore, men and women appear to show differential effects to various antidepressant agents, although more work is needed to precisely define these differences (149, 151, 154).

HIV INFECTION AND ANTIRETROVIRAL THERAPY

The treatment of human immunodeficiency virus (HIV) infection well illustrates the issues of variability in treatment efficacy, toxicity profiles, and drug pharmacokinetics by sex. Multiple studies have shown that women seem to have more frequent and severe side effects with various protease inhibitors (PIs) than do men, including higher rates of GI and neurological side effects with ritonavir, corresponding to higher plasma concentrations of ritonavir in women than men given the same dose (155). Women have a higher incidence of neuropathy and toxicity-driven regimen alterations (156); higher rates of GI disturbances (157); and higher rates of allergic reactions, neurologic side effects, GI problems, and symptoms of nephrolithiasis (158) with PIs than men.

Women also suffer from a greater number of adverse events, such as neuropathy, pancreatitis, and toxicity-driven regimen changes on nucleoside reverse transcriptase inhibitors (NRTIs), than men (159, 160), possibly owing to increased levels of phosphorylation of NRTIs to their active anabolites in women (161). Finally, numerous studies have illustrated an increased incidence of rash with the nonnucleoside reverse transcriptase inhibitor nevirapine (162–164) in women compared to men, likely owing to sex-based pharmacokinetic differences that lead to increased concentrations of nevirapine in women compared to men given the same dose of drug (165).

In addition to the data presented above on toxicity, a few studies have also shown greater efficacy of antiretrovirals in women compared to men, suggesting that sex-based pharmacokinetic differences have pharmacologic consequences. One study showed lower rates of disease progression and hospital admissions secondary to

HIV disease in women initiating highly active antiretroviral therapy (HAART) compared to men in an urban clinic cohort (166). The same group demonstrated that women achieve virologic suppression after starting HAART more quickly than men and sustain a more durable response (167), although a reanalysis by these investigators showed the difference was probably not significant (168). Other groups have shown a slower progression to AIDS and death (169) and a lower risk of progression to AIDS (170) in women on HAART compared to men, although these findings need further elucidation.

Therefore, sex differences in side-effect profiles and a probable difference in efficacy have been demonstrated with antiretroviral agents. Despite these data, a recent meta-analysis that examined 49 randomized, controlled clinical trials of antiretroviral efficacy in adults published from 1990–2000 showed that the proportion of women in the trials was only 12.25%, with analyses by sex performed in only two of the trials (171). Given the accumulating evidence for sex-related differences in responses to antiretroviral agents, more detailed analyses are mandated to explore sex-based pharmacokinetic and pharmacodynamic variability with the use of HIV therapy.

CONCLUSIONS AND DIRECTIONS FOR FUTURE RESEARCH

More and more examples of sex-related differences in pharmacokinetics and pharmacodynamics are emerging. These differences have obvious relevance to the efficacy and side-effect profiles of various medications in men and women. Overall, women have been reported to have a 1.5–1.7-fold greater risk than men of experiencing an adverse drug reaction to medications (172). Despite these increased reports of sex-based differences in adverse drug reactions for drugs already on the market, the evaluation of new drugs in development for differences in efficacy and toxicity by gender has not been fully instituted. Molecular analysis, animal models, and in vivo systems for examining the contributions of various factors, including sex, to drug concentrations in plasma and/or tissues and to pharmacodynamics must be refined and widely applied. Detailed pharmacokinetic and pharmacodynamic studies in both men and women are particularly important for agents used in the treatment of diseases, such as HIV infection, that will require lifelong therapy.

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