

Review

Sex Differences in the Pharmacologic Effects of Antiretroviral Drugs: Potential Roles of Drug Transporters and Phase 1 and 2 Metabolizing Enzymes

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Sex differences in the pharmacologic effects of antiretroviral drugs are increasingly being reported. Emerging evidence suggests that women may be at increased risk of developing adverse effects of antiretroviral drugs. Several mechanisms have been proposed to explain sex differences in drug effects, including physiologic differences between men and women and the influence of sex hormones on drug metabolism. This article reviews sex-related variations in the levels of expression and activities of drug transporters and metabolizing enzymes involved in the disposition of the antiretroviral drugs, and postulates that these variations may partly explain sex differences in the responses to these drugs. Studies that explore relationships between levels of expression and activities of relevant enzymes and drug transporters and observed sex-related differences in treatment responses to antiretroviral drugs will help clarify the extent to which molecules involved in drug disposition affect sex differences in treatment response.

Introduction

The relationship between a patient's sex and that individual's ability to tolerate antiretroviral drugs is increasingly being examined. Several lines of evidence suggest that women are more likely than men to experience adverse effects of antiretroviral drugs.¹ Nevirapine, a non-nucleoside reverse transcriptase inhibitor (NNRTI), is associated with rash and hepatitis more frequently in women than men.²⁻⁶ Protease inhibitor (PI)-associated gastrointestinal intolerance and metabolic disorders are also reported more frequently among women.⁷⁻¹⁰ Boxwell and colleagues¹¹ reported that 83% of 60 cases of lactic acidosis in HIV-infected patients treated with nucleoside reverse transcriptase inhibitors (nRTIs) involved women, and 85% of the 20 fatal cases were in women. Another study¹² examined the relationship between sex

and lipodystrophy in 2258 HIV-infected persons on antiretroviral therapy and found that morphologic alterations were twice as likely in women. These observations suggest that adverse effects may be more frequent in women than in men receiving antiretroviral therapy.

It has been generally presumed that the efficacy of an antiretroviral drug is comparable in men and women. However, 3 recent studies suggest that this may not always be the case. One study from the United Kingdom¹³ evaluated the effectiveness of potent antiretroviral therapy in 91 women and 366 men. Virologic suppression was achieved more rapidly in women, and the response was more durable. A second study¹⁴ evaluated sex differences in the clinical response to antiretroviral therapy in 497 men and 146 women who were observed for more than 13 months. Disease progression occurred in 11% of men and in 8% of women. Hospital admission for an AIDS-defining illness was required for 17% of the men and 12% of the women. A third study,⁹ involving 78 women and 616 men, found that the efficacy of antiretroviral therapy in reducing the plasma HIV-1 RNA concentration was similar for men and women; however, the mean increase in the CD4+ cell count was greater in women (116/ μ L)

than in men (84/ μ L). Although these studies need to be corroborated, the findings suggest that sex may influence the pharmacologic effects of the antiretroviral drugs. Data that indicate increased adverse effects and possibly greater efficacy suggest that women may have better virologic responses to comparable drug doses than do men, or that women may experience higher serum or tissue drug concentrations.

Mechanisms proposed to explain sex differences in drug effects have included physiologic differences in factors such as total body weight, fat distribution, protein binding, gastric motility and acid secretions, glomerular filtration rates, and the influence of sex hormones on drug metabolism. More recently, however, there is growing evidence to suggest that the mechanism of sex-related differences in drug effects may occur at the molecular level. Sex-related variations in the expression and activities of drug transporter genes, proteins, and enzymes involved in phase 1 and 2 biotransformation that form the xenobiotic cascade may underlie some of the observed differences between men and women in responding to certain drugs. This report examines how differences in the expression and activities of these important drug-disposing molecules may explain some of the sex-related differences reported in association with the effects of the antiretroviral drugs.

Antiretroviral Drug Transporters

The drug transporter P-glycoprotein (Pgp) is an important component of the xenobiotic cascade that influences the bioavailability of drugs. Pgp is encoded by the human multidrug resistance (*MDR1*) gene and is constitutively expressed in epithelial cells, especially in tissues important for drug disposition, such as the apical surfaces of intestinal enterocytes, hepato-

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cytes, and proximal renal tubular cells.¹⁵ Expression of Pgp by these tissues reduces drug absorption from the gastrointestinal tract and enhances drug elimination into bile and urine.¹⁶ Because of the key role played by Pgp in drug disposition, sex-mediated differences in its expression and activities could result in differences between men and women in the pharmacologic activities of drugs transported by this molecule.

Recent observations indicate that Pgp influences the disposition of antiretroviral drugs, particularly HIV PIs. Using L-MDR1 and Caco 2 cell lines that overexpress Pgp, Kim and colleagues¹⁷ demonstrated that indinavir, nelfinavir, and saquinavir are transported by Pgp. They also showed that the plasma concentrations of these drugs after oral administration were 2- to 5-fold higher in *mdr1a* knockout mice than in wild-type mice. Another study¹⁸ showed that the transport of saquinavir and ritonavir was 3 times lower across a monolayer of Pgp-enriched Calu-3 cells derived from human airway epithelium than across a similar layer of cells with little Pgp. Several other studies using in vitro models, such as Caco-2 or MDR1-transfected LLC-PK1 cells, have shown that HIV PIs exhibit directional transport.^{19,20} In addition, Pgp inhibitors such as LY-335979, cyclosporin, and verapamil, block cellular transport of HIV PIs, confirming that the PIs are substrates for Pgp.²¹ The regulatory role of drug transporters in the disposition of the HIV nRTIs has not been extensively studied. However, data from 2 studies indicate that the multidrug resistance proteins MRP4 and MRP5 may efflux monophosphate metabolites of nucleoside analogues such as nRTIs from cells.^{22,23}

Given the role of drug transporters in the bioavailability of antiretroviral drugs, in particular the PIs, factors that regulate the expression of these transporters might influence responses to these drugs. Data from animal models and human studies suggest that sex may play a role in the expression of Pgp and other drug transporters. One example of such evidence was provided by Schuetz and colleagues,²⁴ who evaluated the expression of Pgp by hepatic cells in 41 subjects and found that Pgp activity among women was only one third to one half that of men. In another study, involving 36 men and 25 women with

B-cell chronic lymphocytic leukemia, Steiner and colleagues²⁵ showed that women were almost 2 times less likely than men to be positive for the *MDR1* genotype that encodes for Pgp expression. Sex differences in Pgp expression have also been demonstrated in rats²⁶ and Chinese hamsters.²⁷ Sex-dependent expression has been described for other transporters, including sodium taurocholate cotransporting polypeptide (NTCP)²⁸ and the organic cation transporter 2 (OCT2).²⁹ These observed lower expressions of Pgp in women suggest that women might be more likely than men to achieve higher cellular and tissue concentrations of antiretroviral drugs that are Pgp substrates. This may partially explain the increased frequency and severity of adverse reactions and perhaps the enhanced efficacy of some of these drugs in women compared with men.

Antiretroviral Metabolizing Enzymes

Other important components of the xenobiotic disposition pathway that limit the bioavailability of drugs are the drug-metabolizing enzymes. The cytochrome P450 (CYP450) superfamily of enzymes accounts for more than 95% of the phase 1 metabolism of all drugs.³⁰ The CYP450 system consists of at least 11 families of enzymes, of which 3 (CYP1, CYP2, and CYP3) are important in humans. The liver is the primary site of CYP450 activity, but CYP3A is also present in the gastrointestinal enterocytes. CYP3A is the most abundant CYP450 enzyme in the human liver and is responsible for the metabolism of approximately one half of all drugs that undergo phase 1 hepatic metabolism. Phase 2 pathways in drug metabolism include conjugation reactions, such as glucuronidation, sulfation, acetylation, methylation, and glutathione conjugation.

All currently approved HIV PIs are metabolized by CYP450 isoforms. Fitzsimmons and Collins³¹ demonstrated the in vitro biotransformation of saquinavir by intestinal and hepatic microsomes to multiple hydroxylated derivatives and also showed that CYP3A4 was the main enzyme involved in the biotransformation. CYP3A4 is also responsible for the metabolism of indinavir,³² amprenavir,³³ nelfinavir,³⁴ and

lopinavir.³⁵ Ritonavir is metabolized primarily by CYP3A4 and, to a lesser extent, by CYP2D6 and CYP2C9.³⁶

The CYP450 enzyme system is also responsible for the biotransformation of the NNRTIs. In vitro studies of nevirapine biotransformation have demonstrated that the isoenzymes CYP2B6 and CYP3A4 metabolize nevirapine, with CYP2D6 playing a minor role.³⁷ The isoenzyme primarily responsible for the biotransformation of efavirenz is CYP2B6, with some involvement by CYP3A4.³⁸ Delavirdine is metabolized primarily by CYP3A4 and, to a lesser extent, by CYP2D6.³⁹ Many PI and NNRTI metabolites generated by CYP450 biotransformation subsequently undergo phase 2 reactions before being eliminated in urine or bile.

The nRTIs, on the other hand, are eliminated unchanged in the urine, or undergo hepatic glucuronidation prior to excretion in urine or bile.⁴⁰⁻⁴⁴ Changes in plasma concentrations of the nRTIs, however, may be of less clinical relevance than for PIs and NNRTIs, because their antiviral effects mainly depend on the rate and extent of intracellular phosphorylation by cellular kinases into triphosphate derivatives.⁴⁵ The intracellular accumulation of nRTI mono- or diphosphates resulting from rate-limiting steps in this phosphorylation pathway could be responsible for some of the toxic effects of the drugs, particularly within mitochondria.⁴⁶

Knowledge is growing about sex differences in regulating the expression and activity of phase 1 and phase 2 drug-metabolizing enzymes, which are probably related to endogenous sex hormones.⁴⁷ Activities of CYP1A2 and CYP2E1 may be higher in men than in women,⁴⁸⁻⁵¹ whereas CYP2D6 activity may be higher in women than in men.⁵² Sex differences in CYP2C19 activity appear to show ethnic variations: CYP2C19 activity is higher in Chinese, Jewish-Israeli, and African American women than in men of these ethnic backgrounds.⁵³⁻⁵⁵ No sex difference in the activity of CYP3A seems to exist.⁵⁶ Although hepatic clearance of drugs that are substrates for both CYP3A and Pgp (such as erythromycin and verapamil) appears to be higher in women than in men, this may be explained largely by lower hepatic Pgp activity in women.⁵⁷⁻⁵⁹

The activities of some phase 2 isoen-

zymes also exhibit sex differences. Thiopurine methyltransferase (TPMT) activities are 14% lower in liver tissues from women than from men.⁶⁰ Similarly, levels of catechol-O-methyltransferase activity are lower in women.⁶¹ The activity of several isoenzymes of the uridine 5-diphosphate glucuronosyltransferase (UGT) superfamily, including UGT1A1, UGT1A6, UGT1A8, UGT1A9, and UGT1A10, is also lower in women.⁶²⁻⁶⁵ A study from Finland shows that phenol sulfotransferase activity is more than 60% lower in women than men.⁶⁵ Sex differences in regulation of the activities of the cellular kinases that activate nRTIs remain undefined.

Based on available studies, enzymes involved in phase 1 reactions may have only a limited role, if any, in the sex-related differences in pharmacologic effects of the antiretroviral drugs. The activity of CYP3A, the principal isoform of the CYP450 system, in the biotransformation of PIs and NNRTIs does not appear to be influenced by sex. Although CYP2D6 activity is reported to be higher in women than in men, the role of this isoform in the metabolism of ritonavir and delavirdine is limited. In contrast, activities of many isoenzymes involved in phase 2 reactions are lower in women than in men, suggesting that antiretroviral agents (or their metabolites) that undergo biotransformation by these pathways may reach higher concentrations in the cells and tissues of female HIV patients than in male patients.

Sex differences in the activities of cellular kinases that activate nRTIs remain unclear. Studies to explore sex differences in the expression and activities of these key enzymes in the metabolism of the nRTIs will be of interest for 2 reasons. First, there are documented sex differences between men and women in the development of adverse effects associated with the nRTIs, in particular, lactic acidosis. Second, both the efficacy and the toxic effects of the nRTIs are related to the phosphorylated products of the cellular kinases.

Conclusion

HIV infection has become a chronic, treatable illness, especially in the developed countries, as many HIV-infected patients are on antiretroviral therapy and

are living longer. The adverse effects of these drugs, particularly in women, are a growing source of concern, because many observational studies have shown that women experience greater toxic effects with all classes of antiretroviral drugs. Although sex differences in the effects of these drugs may be due in part to physiologic and hormonal differences between men and women, variations in the activities of drug transporters and metabolizing enzymes involved in phase 1 and 2 reactions may also be involved. Further studies are needed to relate activities of these enzymes and drug transporters and observed sex differences to the effects of the antiretroviral drugs. Such studies will enhance our ability to develop new agents that are better tolerated by both sexes, and to identify drug dosages that are most effective for women.

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