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Implications of gender and pregnancy for antiretroviral drug dosing

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Abstract

Purpose of review—This review briefly outlines the influences of gender and pregnancy on drug disposition, and describes the available antiretroviral pharmacokinetic data and dosing recommendations in these groups.

Recent findings—Recent studies in pregnant women continue to document altered exposure of different classes of drugs during pregnancy. While new information shows that tenofovir exposure is significantly decreased during pregnancy, the magnitude of the decrease will not likely necessitate dose changes, similar to other nucleoside reverse transcriptase inhibitors. In contrast, standard doses of lopinavir/ritonavir in the third trimester showed markedly decreased exposure, and higher doses of this co-formulated agent should be given to women during the third trimester. Likewise, nelfinavir exposure using the new 625-mg tablets is also decreased during pregnancy, and higher doses should be considered in the third trimester.

Summary—The majority of antiretrovirals studied have altered pharmacokinetics during pregnancy. Understanding the extent of these changes is necessary to recommend dose changes during pregnancy when appropriate. The correct dose is critical to maintain efficacy and safety of these agents for both the mother and the fetus. Innovative study designs are needed to facilitate the study of antiretrovirals during pregnancy.

Keywords

antiretroviral; gender; pharmacology; pregnancy

Introduction

Infection with HIV is a major contributor to global morbidity and mortality. The estimated number of people living with HIV infection worldwide at the end of 2006 was approximately 40 million, including 18 million women and 2.3 million children [1*]. Most of the infected women are of childbearing age. Antiretroviral treatment in pregnant women may have two goals: preventing HIV transmission to the child, and treating the mother's underlying disease. This review briefly outlines how gender and pregnancy may influence drug disposition, and describes the available pharmacokinetic data for antiretrovirals in pregnant women.

Gender effects on drug disposition

Gender can be a significant determinant of therapy response through its impact on drug disposition. In addition to the influence of gender on body size and composition, differences exist between men and women in gastrointestinal physiology, drug metabolism, excretion and protein binding. While large gender differences in drug metabolism are seen in rodents, these effects are much less pronounced in humans. Modest increased cytochrome (CYP) P450 3A activity is seen in women but appears to be substrate specific, and confounded by gender effects on body size and drug absorption [2–5]. Individual studies have found women to have modest increases in plasma concentrations for saquinavir, ritonavir, efavirenz, nevirapine, enfuvirtide and lopinavir; however, these studies have not been prospectively designed to characterize the specific impact of gender on pharmacokinetics [6–10]. Regardless of the mechanism responsible for enhanced exposure, higher saquinavir and ritonavir concentrations seen in women have been associated with improved virologic response [11] or increased side effects [12]. While men and women have similar systemic pharmacokinetics for the nucleoside reverse transcriptase inhibitors, higher intracellular zidovudine and lamivudine triphosphate concentrations have been seen in women [13].

Pregnancy effects on drug disposition

Pregnancy causes physiologic changes that significantly affect all aspects of drug disposition – absorption, distribution, metabolism and excretion. Absorption may be decreased by the nausea and vomiting associated with pregnancy, especially in the first trimester. Increases in plasma progesterone during pregnancy correspond to decreases in gastrointestinal motility, with prolonged gastric emptying and intestinal transit times, which may lead to delayed drug absorption and reduced peak concentrations [14]. Gastric pH is increased during pregnancy, as gastric-acid secretion is reduced, which may affect the ionization and absorption of weak acids and bases [15].

Total body water expands by about 8 l; plasma volume increases by 50%, and body-fat stores increase during an average pregnancy [16]. This generally increases the volume of distribution and decreases the maximum concentration of both hydrophilic and lipophilic drugs. Competitive inhibition from steroid hormones and decreased albumin from dilution cause a decrease in protein binding and a corresponding increase in the free fraction or pharmacologically active component of drugs during pregnancy [17,18].

Changes in drug metabolism during pregnancy are variable. Activity of CYP P450 2C, 2D6 and 3A enzymes increases, while the activity of CYP 1A2 decreases [19,20]. Renal plasma flow and glomerular filtration rate increase by 25–50% [15]. This enhanced renal function increases the clearance of renally eliminated drugs in pregnancy.

The physiologic changes during pregnancy will affect the disposition of most drugs; however, the need for dose changes during pregnancy will depend on the magnitude and complexity of pharmacokinetic and pharmacodynamic alterations. As pharmacokinetic studies are difficult to perform in pregnancy, published data on drug disposition are limited and rarely provide clinically relevant dosing guidelines [21].

Nucleoside/nucleotide reverse transcriptase inhibitors

Nucleoside reverse transcriptase inhibitors are metabolized intracellularly to the active triphosphorylated forms. These nucleotides compete with endogenous nucleotides and inhibit HIV reverse transcriptase, preventing viral replication [22]. The half-life of intracellular triphosphorylated nucleotides is usually longer than that of the parent drug in the plasma, allowing for once or twice-daily dosing [23].

Abacavir

A study of 25 women taking abacavir 300 mg twice daily during pregnancy and postpartum found overall AUC_{0-12} to be similar at both time points, and also similar to nonpregnant historical controls [24]. These subjects did have significantly lower maximum concentrations during pregnancy, and increased 6-h concentrations, suggesting a delay in absorption during pregnancy. Cord-blood abacavir concentrations averaged 100–110% of maternal plasma concentrations at delivery [24,25]. No abacavir dose adjustments due to pregnancy are necessary.

Didanosine

Didanosine intravenous and buffered capsule pharmacokinetics were studied in nine pregnant women during pregnancy and postpartum [26]. Clearance of intravenous doses was significantly higher during pregnancy. Bioavailability of buffered capsules was tremendously variable (from 15% to 84%), and no difference in oral clearance was noted between pregnancy and postpartum, although the huge variability in bioavailability may have masked a more modest difference in oral clearance. Transfer of didanosine through the placental barrier is only about 40%, lower than for the other nucleoside reverse transcriptase inhibitors [25,27]. The current enteric-coated capsule formulation of didanosine needs to be studied in pregnant women.

Emtricitabine

No human pharmacokinetic data are available for emtricitabine in pregnancy. It is predominantly eliminated unchanged in the urine, and elimination may be enhanced by typical renal function changes in pregnancy. Animal and ex-vivo studies suggest that these drugs passively diffuse into the placenta [28,29].

Lamivudine

A study of 20 South African women showed no significant differences in lamivudine pharmacokinetics between the 38th week of gestation and the first week after delivery [30]. Lamivudine crosses the placenta by simple diffusion, with approximately equal concentrations in the cord blood and maternal plasma [25,31,32]. Standard adult doses of lamivudine should be used in pregnant women.

Stavudine

Stavudine pharmacokinetics in 14 pregnant women were similar to values reported in nonpregnant historical controls [33]. Placental transfer was high, with cord-blood concentrations about 130% of maternal plasma concentrations at delivery [25,33]. No stavudine dose adjustments due to pregnancy are required.

Tenofovir

There is a recent preliminary report of 19 women taking 300 mg once daily of tenofovir in the third trimester of pregnancy and at 6–12 weeks postpartum [34*]. Peaks, troughs and AUC_{0-24} were significantly lower during the third trimester compared to postpartum. The magnitude of the AUC decrease in pregnancy was only about 15%, however. Median cord blood to maternal plasma concentration ratios were about 1, ranging from 0.6 to 1.7 [34*, 35*]. While tenofovir exposure is lower during pregnancy, standard dosing results in sufficient exposure for most women, and a dose modification for pregnancy is not recommended.

Zidovudine

Zidovudine was the first drug proven to decrease mother-to-child HIV transmission, and is widely used in pregnant women worldwide [36,37]. Several studies have shown that zidovudine maximum concentrations, half-life and bioavailability do not differ during pregnancy compared with nonpregnant adults [30,38–40]. Within-subject comparisons of women during pregnancy and at 1–4 weeks postpartum show significantly increased oral clearance by 47–65% and decreased AUC by 34–39% during pregnancy [30,38]. Zidovudine crosses the placenta by simple diffusion, with approximately equal concentrations in the cord blood, the amniotic fluid, and the maternal plasma [30,38,41]. Standard regimens of 200 mg three times daily or 300 mg twice daily are generally recommended in pregnant women.

Nonnucleoside reverse transcriptase inhibitors

Nonnucleoside reverse transcriptase inhibitors bind directly to HIV reverse transcriptase, noncompetitively inhibiting its activity. They do not require intracellular phosphorylation or other activation. Three highly potent agents are available: delavirdine, efavirenz and nevirapine, but since rapid high-level resistance can develop with a single point mutation, these are generally used only as part of combination regimens [42].

Nevirapine

Several small studies have described the pharmacokinetics of chronic administration of nevirapine to pregnant women. Three studies have shown similar or slightly increased oral clearance during pregnancy compared with postpartum or historic data in nonpregnant adults [43,44]. A recent study evaluated nevirapine pharmacokinetics on the day of scheduled caesarean section in 20 women who had been taking a nevirapine-containing regimen during pregnancy [45]. The median minimum concentration on the day of delivery was 2.6 µg/ml (range 1.4–3.8 µg/ml). Many women were below the suggested trough for nevirapine of 3 µg/ml.

Pharmacokinetics of single-dose nevirapine in late pregnancy before labor onset are equivalent to those seen in nonpregnant adults [46]. When single doses are administered during labor, however, the pharmacokinetics of nevirapine are significantly different, with increased oral clearance, half-life, and apparent volume of distribution, and decreases in AUC and maximum concentration [46–48]. Nevirapine crosses the placenta rapidly and effectively. Cord-blood concentrations are approximately 1000 ng/ml after single maternal doses during labor, with cord-blood/maternal plasma concentration ratios at delivery of approximately 80% [49]. With chronic maternal dosing in the third trimester, average cord-blood concentrations are 2000 ng/ml [50]. The standard dose schedule for nevirapine is recommended in pregnancy.

Delavirdine and efavirenz

Delavirdine and efavirenz are teratogenic to laboratory animals, with severe neural-tube defects in primates receiving efavirenz early in pregnancy [51,52]. An infant exposed to efavirenz *in utero* had a neural-tube defect [53]. No human pharmacokinetic data are available for efavirenz or delavirdine in pregnancy.

Protease inhibitors

Protease inhibitors are potent antiretrovirals that inhibit the HIV protease enzyme, leading to the release of structurally disorganized and noninfectious viral particles. They are metabolized mainly by CYP3A, and also by CYP2C9, CYP2C19, and CYP2D6 [54].

Protease inhibitors can induce, inhibit or both induce and inhibit drug-metabolizing enzymes, causing complex drug interactions in this class. Except for indinavir, protein binding is greater than 85% for available agents. They are lipophilic, substrates for many transporters and generally have poor bioavailability. Protease inhibitors have limited placental transfer, suggesting that maternal protease-inhibitor therapy during labor will not provide postexposure prophylaxis to the newborn at birth [45,55,56,57*,58**]. No pharmacokinetic data are available during pregnancy for newer protease inhibitors including amprenavir/fosamprenavir, tipranavir and darunavir.

Atazanavir

A recent study of nine women taking atazanavir 300 mg with ritonavir 100 mg once daily during pregnancy and postpartum reported similar pharmacokinetics at both times, and suggests that no dose adjustment is needed in pregnancy [59*]. Transfer from maternal plasma to cord blood was approximately 13%.

Indinavir

Published studies of indinavir during pregnancy are limited. In a report of two women taking 800 mg three times daily throughout pregnancy, AUC_{0-8} was reduced by more than 60% during the third trimester compared with 9–12 weeks postpartum [60]. Another study of 16 women showed considerable variability and significantly decreased maximum concentrations and AUC_{0-8} during the third trimester compared with 6 weeks postpartum [61**]. Use of standard dose indinavir is likely suboptimal in pregnancy and should be avoided. Pharmacokinetics of ritonavir-boosted indinavir during pregnancy should be studied.

Lopinavir

Lopinavir is a protease inhibitor available only in a fixed combination with low-dose ritonavir (Kaletra). In a study of 17 pregnant women taking the standard dose using the capsule formulation (400 mg lopinavir with 100 mg ritonavir twice daily), mean lopinavir AUC_{0-12} during the third trimester was approximately half of the values seen in nonpregnant adults, and was significantly lower than the AUC_{0-12} observed in these same women at 6–12 weeks postpartum. Fourteen of 17 women had AUC_{0-12} less than the estimated 10th percentile lopinavir AUC expected in nonpregnant adults [62]. Another study of 26 pregnant women taking the standard dose measured trough concentrations during the third trimester, and reported that four women had subtherapeutic troughs (range 425–1106 ng/ml), and the median trough in all women was 2964 ng/ml [63*]. A study of 26 pregnant women evaluated an increased dose (533 mg lopinavir with 133 mg ritonavir) during the third trimester of pregnancy, continuing until 2 weeks after delivery [64]. This increased dose in the third trimester yielded a median AUC similar to that in nonpregnant adults. The AUC at 2 weeks after delivery on this increased dose was 72% higher, however. Several women taking the standard dose during the second trimester had a modestly reduced AUC (median of 57 μ g h/ml). Taken together, increased lopinavir doses should be prescribed during the third trimester, and should be considered in the second trimester in patients with extensive protease inhibitor exposure and suspected resistance mutations. Doses should be decreased back to standard before 2 weeks after delivery. Since the capsule formulation of lopinavir is no longer available, the tablet formulation at a higher dose (600 mg/200 mg twice daily) in the third trimester of pregnancy is currently being evaluated.

Nelfinavir

Nelfinavir has been the most common protease inhibitor used in pregnancy because of its tolerability, safety and potency. The pharmacokinetics have been studied in pregnant women

receiving 750 mg three times daily and 1250 mg twice daily. With the 250-mg tablet formulation, nine women taking thrice-daily nelfinavir had low AUCs, with two-thirds of the women below the estimated 10th percentile AUC in nonpregnant adults [65]. In 21 women taking twice-daily nelfinavir, exposure was improved and similar to nonpregnant adults, with only four women falling below the AUC target exposure [66]. Within-subject comparisons between pregnancy and postpartum showed significant postpartum increases in maximum concentration and AUC, and decreases in oral clearance and the ratio of its active metabolite to the parent drug concentration [66,67]. Two recent studies of 25 and 27 pregnant women taking nelfinavir 1250 mg twice daily showed significantly lower troughs, peaks and AUC and higher oral clearance in the third trimester compared with the same women 6–12 weeks postpartum [68] or nonpregnant controls [69]. Doses of 750 mg three times daily should be avoided in pregnancy. A dose of 1250 mg twice daily yields lower exposure during the third trimester than in nonpregnant adults and higher doses or monitoring of trough nelfinavir concentrations should be studied.

Saquinavir

A study of four women taking saquinavir soft-gelatin capsules, 1200 mg three times daily, showed an average AUC_{0-8} of 1672 $\mu\text{g h/ml}$ in pregnancy, as compared with 7249 $\mu\text{g h/ml}$ in nonpregnant adults, and the protocol was stopped [70]. Similarly, a study of nine pregnant Thai women found an AUC_{0-8} of 2630 $\mu\text{g h/ml}$ [71]. Cord-blood and newborn-plasma concentrations at delivery in these studies were mostly undetectable [70,71]. A study of 13 pregnant women taking ritonavir-boosted saquinavir (800 mg saquinavir and 100 mg ritonavir twice daily) showed AUC_{0-12} during the third trimester, at delivery and postpartum similar to that seen in nonpregnant adults [72]. A recent study of 45 pregnant women taking 1200 mg saquinavir hard-gel capsules with 100 mg ritonavir once daily reported trough greater than the target of 100 ng/ml in all but three subjects, who required a 1600 mg/100 mg dose once daily [73**].

Conclusion

Gender influences exposure to some antiretrovirals. Additionally, the profound physiologic changes associated with pregnancy significantly affected most antiretrovirals studied, usually leading to decreased exposure during pregnancy. Traditional phase I studies are difficult to perform in pregnant women for ethical and practical reasons, leading to a paucity of published information, especially for newer agents. New and innovative methods are necessary to assess both pharmacokinetics and safety of antiretrovirals in pregnant women to allow safe and effective use of these drugs for the mother and the fetus.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 404).

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