Effects of Gender, Pregnancy, and Anesthesia on the Pharmacokinetics of Zidovudine in Rats

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Purpose. The effects of gender, pregnancy and anesthesia on the pharmacokinetics of zidovudine (AZT) were studied in rats.
Methods. Unanesthetized male (MR), female (FR) and pregnant (day 20, PR) rats received 50 mg/kg AZT via a jugular vein cannula. Female (FRA), pregnant (day 20, PRA) and pregnant (day 20, PRR) rats maintained under ketamine: acepromazine:xylazine anesthesia also received 50 mg/kg AZT. Two fetuses were removed at each sampling time from the PRR group. Plasma samples were collected and analyzed by RIA.
Results. With the exception of a lower non-renal clearance in female rats, there were no gender differences in the disposition of AZT. No significant differences were noted in total clearance, non-renal clearance or volume of distribution between pregnant and female rats, however, significant differences in renal clearance values were evident. Anesthesia resulted in decreased total, renal and non-renal clearances in female and pregnant rats. The removal of fetuses during the experiments did not alter the total clearance of AZT in pregnant rats, however, renal clearance and volume of distribution were decreased by cesarian section.
Conclusions. The rat appears to be a suitable laboratory animal model for investigating AZT disposition during pregnancy. However, results of pharmacokinetic studies when animals are maintained under anesthesia with ketamine:acepromazine:xylazine must be interpreted with caution.

KEY WORDS: zidovudine; gender; anesthesia; pregnant; pharmacokinetics; rats.

INTRODUCTION

Acquired immunodeficiency syndrome (AIDS) resulting from infection by the human immunodeficiency virus (HIV) was first reported in 1981 (1) with the majority of AIDS patients being male. However, HIV infection in women, particularly those of child-bearing age, has increased significantly over the past several years with over 30,000 cases of HIV infected female patients reported to the Centers for Disease Control (2). Furthermore, the increasing cases of infection of infants by maternal transmission of HIV has become a serious problem. The vertical transmission of HIV appears to be as high as 30% in human infants born to infected mothers (3). Thus, the increasing of HIV infection in women and infants by maternal-fetal transmission of HIV has become a perilous epidemic.

Treatment of HIV infected women and prevention of the vertical transmission of HIV is paramount to abrogating pediatric AIDS. Zidovudine (AZT) was the first anti-HIV drug approved for use and remains the most widely used agent for the treatment of HIV infection (4-7). An interim analysis of a clinical trial to test if AZT can prevent HIV-infected pregnant women from transmitting the virus to their infants found a two-thirds reduction in risk among those who received the drug (8). AZT, when administered during labor, appeared to be well tolerated by both the pregnant mothers and their newborns, although some minor transitory toxicity of AZT on fetal hematopoiesis has been reported (5,6). The pharmacokinetics of AZT in women, particularly during pregnancy, however, are inadequately defined.

Gender-related differences in drug pharmacokinetics are well known and are found in both laboratory animals and humans (9,10). Furthermore, pregnancy has been known to change various physiological functions and to alter the pharmacokinetics of drugs (11,12). Since it is difficult to study drug disposition during pregnancy in clinical trials, an animal model may provide the basic information that can be clinically useful. Recent reports which have utilized monkeys as an animal model have contributed to the understanding of the maternal-fetal transfer of AZT (13,14). However, much remains to be learned and the monkey model may not be suitable, for a variety of reasons, for many mechanistic investigations. Thus, an animal model to examine the basic mechanisms involved in the maternal-fetal transfer of nucleoside analogues remains to be established. Since the hemochorial placenta and the hemodynamic changes in pregnant rats are similar to those in humans, the rat appears to be a suitable model for studying the effects of pregnancy on drug disposition. The rat model has been employed for examining drug disposition during pregnancy (15) and has proven to be an effective animal model for investigating the disposition of nucleoside analogues (16).

The objective of this study was to develop the pregnant rat model for the investigation of AZT pharmacokinetics during pregnancy. The effects of gender and pregnancy on the disposition of AZT in the rat was examined. Anesthesia is often induced in laboratory animals to perform surgery or to manipulate experimental procedures. Anesthetic agents have been found to alter hemodynamics and to affect the pharmacokinetics of drugs (17,18). Hence, the effect of anesthesia on the disposition of AZT in female and pregnant rats was also investigated.

MATERIALS AND METHODS

Chemicals

Zidovudine was purchased from Sigma Chemical Co. (St. Louis, MO). ZDV-Trac ^{125}I RIA kit was purchased from Incstar Corp. (Stillwater, MN). All other chemicals, HPLC or reagent grades, were purchased from J. T. Baker Inc. (Phillipsburg, NJ).

Animal Experiments

Rats were maintained at the University of Georgia College of Pharmacy Animal Care Facility, which is fully accredited by the American Association for the Accreditation

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of Laboratory Animal Care (AAALAC). Animal studies were approved by the University of Georgia Animal Care and Use Committee, and conducted in accordance with guidelines established by the Animal Welfare Act and the National Institutes of Health *Guide for the Care and Use of Laboratory Animals*. Six groups of Sprague-Dawley rats were used in the study. The first three groups, male rats (MR) weighing 272 ± 17 g (n = 6), female rats (FR) weighing 248 ± 16 g (n = 6) and pregnant rats (PR), weighing 389 ± 38 g (n = 6) were conscious during the experiment. The fourth group, female rats (FRA), weighed 281 ± 10 g (n = 6) and were maintained under anesthesia during the experiment. The fifth group, pregnant rats (PRA), weighed 411 ± 28 g (n = 6) and were maintained under anesthesia during the experiment. The sixth group, pregnant rats (PRR), weighing 412 ± 20 g (n = 4) were maintained under anesthesia and 2 pups were removed by cesarian section at each blood sampling time.

Female rats were placed individually in cages with male breeders. The day vaginal plugs were found was considered day 1 of pregnancy. On day 20 (term = 21 to 23 days) of pregnancy, the experiment was performed. For all surgical procedures and experiments which required anesthesia, rats were maintained under anesthesia by ketamine:acepromazine:xylazine (50:3.3:3.4 mg/kg) administered intramuscularly. Body temperature of anesthetized rats was maintained at 37°C by a heating pad. For the rats which were conscious during the experiment, a right jugular vein cannula was surgically placed the day before the experiment. For rats which were maintained under anesthesia during the experiment, the cannula was implanted just prior to the experiment. All rats were fasted for 8 h prior to the study, however water was freely available. Food was made available again at 10 h after drug administration.

Rats were administered 50 mg/kg AZT dissolved in 1 ml normal saline over 1 min via the cannula. Blood (0.3 ml) samples were collected through the cannula prior to and 0.08, 0.25, 0.5, 1, 2, 3, 4, 6, 8 and 10 h after drug administration. Previous studies demonstrated no adsorption of AZT to cannulas (16). Blood volume was replaced with an equal volume of normal saline. Blood samples were immediately centrifuged and plasma was frozen at -20°C until analysis. Urine samples were collected periodically for 24 h, urine volume was recorded and samples were frozen at -20°C until analysis.

Zidovudine Analysis

Concentrations of AZT in plasma samples were determined by using the Incstar ZDV RIA kit (Incstar Corp., Stillwater, MN). Samples were diluted with the sample diluent to fall within the standard curve range. The lower limit of quantitation was 0.5 ng/ml. Intra- and inter-day relative standard deviations for the assay were less than 10%. The urine samples were assayed by high performance liquid chromatography (HPLC) as previously described (16). Preliminary studies demonstrated that HPLC and RIA analysis yield identical results.

Pharmacokinetic Analysis

The disposition of AZT was described in terms of the SHAM properties of the plasma AZT concentration versus time curves (19). Plasma concentrations of AZT in all 6 groups of rats were best described by a biexponential decline (20). The AZT concentration (C) versus time (t) data was analyzed by PCNONLIN weighted (1/C) least-squares regression (21). The area under the plasma concentration-time curve (AUC) and first moment curve (AUMC) were calculated by $C_1/\lambda_1 + C_2/\lambda_2$ and $C_1/\lambda_1^2 + C_2/\lambda_2^2$, respectively. Total clearance (CL_T) was calculated from dose/AUC. The fraction excreted unchanged in the urine (f_e) was calculated by dividing the total amount of AZT excreted by the dose. Renal clearance (CL_R) was determined from $f_e \times CL_T$ and nonrenal clearance (CL_{NR}) from $CL_T - CL_R$. The mean residence time (MRT) was calculated as AUMC/AUC and steady-state volume of distribution (V_{SS}) was determined from $CL_T \times MRT$. The terminal half-life ($t_{1/2}$) was calculated from $0.693/\lambda_2$.

Statistical analysis comparing the pharmacokinetic parameters of male and female rats was performed by using the t-test. A two-way analysis of variance (ANOVA) was used to compare the effects of pregnancy and anesthesia. Statistical analysis assessing the effects of removing pups from pregnant rats was performed by using the t-test. P values less than 0.05 were considered statistically significant. A power analysis demonstrated a power of greater than 80% of all statistical comparisons.

RESULTS

Plasma AZT concentrations following intravenous administration of 50 mg/kg AZT to male and female rats are shown in Fig 1. AZT concentrations in these two groups of rats were superimposable. Pharmacokinetic parameters for the MR and FR groups are presented in Table I. There were no significant differences in $t_{1/2}$, MRT, CL_T, CL_R, or V_{SS} between the MR and FR groups. However, CL_{NR} was significantly lower in the female rats than in the male rats while f_e was greater in the FR group.

Figure 2 illustrates the plasma AZT concentration versus time profiles after administration of AZT to the FR, PR, FRA, and PRA groups. Plasma concentrations of AZT in the PR group of rats were greater than those of the FR group (Fig. 2), and the terminal phase half-life was approximately 50% longer in the FR group (Table I). Similarly, AZT plasma concentrations in the PRA groups of rats were greater than

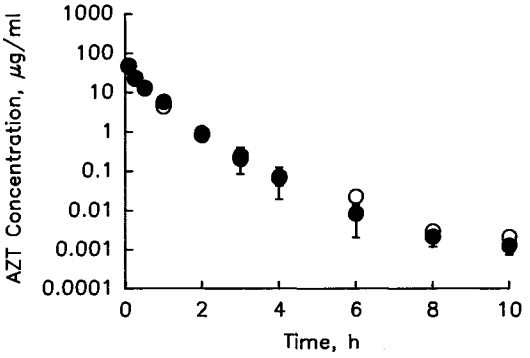

Fig. 1. Plasma concentrations (mean ± SD) of AZT after intravenous administration of 50 mg/kg AZT to conscious male (○, MR) and female (●, FR) rats.

Table I. Pharmacokinetic Parameters (SD) of AZT Following Intravenous Administration of 50 mg/kg AZT to Conscious Male Rats (MR), Conscious Female Rats (FR), Conscious Pregnant Rats (PR), Female Rats Maintained Under Anesthesia (FRA), Pregnant Rats Maintained Under Anesthesia (PRA), and Pregnant Rats Maintained Under Anesthesia with 2 Pups Removed by Laparotomy at Each Sampling Time (PRR)

Parameter	MR	FR	PR	FRA	PRA	PRR
C_1, μg/ml	40.71	46.10	62.31	77.58	70.92	169.73
	(4.95)	(22.12)	(15.13)	(54.03)	(14.66)	(156.26)
λ_1, h^{-1}	2.41	2.92	2.03^{P}	3.49	0.81^{P}	9.01
	(0.43)	(1.95)	(0.81)	(2.89)	(0.12)	(9.85)
C_2, μg/ml	1.32	5.18	4.97	17.61	3.10	69.59^{R}
	(0.60)	(8.96)	(7.89)	(22.48)	(2.16)	(20.59)
λ_2, h^{-1}	0.75	0.81	0.51^{P}	0.49^{A}	0.30^{PA}	0.60^{R}
	(0.10)	(0.37)	(0.16)	(0.17)	(0.10)	(0.07)
$t_{1/2}$, h	0.94	1.02	1.54^{P}	1.64^{A}	2.78^{PA}	1.16
	(0.12)	(0.40)	(0.62)	(0.66)	(1.41)	(0.14)
AUC, μg/ml * h	18.96	20.99	41.23^{P}	65.18^{A}	98.59^{PA}	145.95^{R}
	(2.25)	(4.50)	(9.96)	(14.41)	(22.11)	(28.51)
MRT, h	0.51	0.53	0.74^{P}	1.09^{A}	1.45^{PA}	1.40
	(0.06)	(0.09)	(0.13)	(0.24)	(0.28)	(0.10)
CL_T, L/h	0.74	0.65	0.52	0.24^{A}	0.23^{A}	0.15
	(0.13)	(0.17)	(0.19)	(0.077)	(0.072)	(0.035)
CL_R, L/h	0.40	0.44	0.35^{P}	0.20^{A}	0.15^{PA}	0.083^{R}
	(0.095)	(0.11)	(0.15)	(0.091)	(0.012)	(0.041)
CL_{NR}, L/h	0.34	0.21^{G}	0.16	0.058^{A}	0.056^{A}	0.062
	(0.057)	(0.090)	(0.046)	(0.022)	(0.0059)	(0.0097)
f_e	0.54	0.68^{G}	0.67	0.77^{A}	0.73^{A}	0.55
	(0.05)	(0.08)	(0.04)	(0.04)	(0.03)	(0.16)
V_{SS}, L	0.37	0.35	0.37	0.25	0.32	0.20^{R}
	(0.045)	(0.11)	(0.086)	(0.089)	(0.081)	(0.036)

^{G} statistically significant effect of gender; ^{P} statistically significant effect of pregnancy; ^{A} statistically significant effect of anesthesia; ^{R} statistically significant effect of removing pups.

those of the FRA group. The corresponding pharmacokinetic parameters are presented in Table I. Since the weight gain associated with pregnancy (approximately 50%) would not be expected to affect drug elimination, clearance values are reported as non-weight normalized values. Intercept values C_1 and C_2 were similar in these groups of rats. Statistically significant differences were noted in λ_1 and λ_2 values between the female and pregnant groups (Table I). No significant differences were noted in CL_T, CL_{NR} and V_{SS} between pregnant and female rats. However, pregnancy resulted in a significant decrease in CL_R (Table I).

As seen in Fig. 2, the plasma AZT concentrations of the rats which were maintained under anesthesia (FRA and PRA) were higher than those of the conscious animals (FR and PR). Anesthesia produce significant differences in λ_2 and corresponding $t_{1/2}$ values (Table I). Statistically significantly lower CL_T, CL_R, and CL_{NR} were noted in anesthetized rats than in conscious rats (Table I). No differences were seen in steady state volume of distribution values. No interactions between pregnancy and anesthesia were observed in any of the pharmacokinetic parameters.

Plasma AZT concentrations after administration of AZT to pregnant rats maintained under anesthesia with 2 pups removed by laparotomy at each sample time (PRR) are also shown in Fig 2. AZT concentrations in the PRR group were slightly greater than those of the PRA group. Surgical removal of pups resulted in significant differences in C_2, λ_2, AUC, CL_R and V_{SS} values between the PRA and PRR rats. No differences were noted in CL_{NR} or CL_T values.

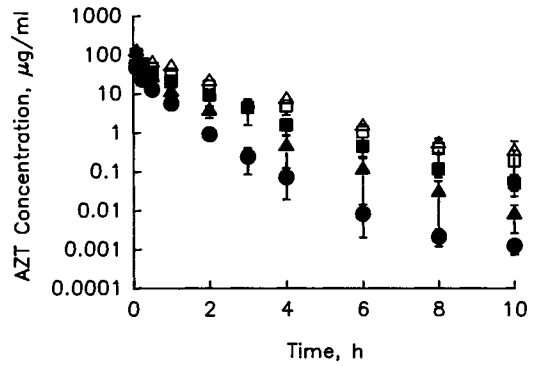

Fig. 2. Plasma concentrations (mean ± SD) of AZT after intravenous administration of 50 mg/kg AZT to conscious female rats (●, FR), conscious pregnant rats (▲, PR), female rats maintained under anesthesia (■, FRA), pregnant rats maintained under anesthesia (□, PRA), and pregnant rats maintained under anesthesia with 2 pups removed by laparotomy at each sampling time (△, PRR).

DISCUSSION

The pharmacokinetic profiles of AZT in male rats found in the present study corresponded well to those which were previously reported (16). Renal clearance of AZT was similar in male and female rats, however, non-renal clearance of the drug was approximately 30% lower in the female rats. The primary non-renal clearance mechanism for AZT in the

rat is metabolic reduction of the 3'-azido group yielding an amino moiety (22). Sex-dependent metabolism of xenobiotics in rats has been observed for numerous substrates of phase I and phase II metabolic pathways (9,10). In general, if gender differences exist, metabolic activities in male rats tend to be greater than in female rats (10). These metabolic differences have been attributed to expression of sex-specific P-450 isoenzymes (9). The slower non-renal clearance of AZT in female rats resulted in a greater fraction of the drug being excreted unchanged in urine of female rats. The gender difference in non-renal clearance of AZT was not large enough to induce differences in total clearance of the nucleoside. Furthermore, the distribution of AZT was not influenced by the gender of the rat. Thus, the overall disposition characteristics of AZT in male and female rats were comparable. Similarly, no differences in the pharmacokinetics of AZT between male and female human patients has been reported (4).

An interim analysis of a trial of AZT in pregnant women suggests that the nucleoside may be effective in preventing HIV-infected pregnant women from transmitting the virus to their infants (8). Orally administered AZT is initiated at 14 to 34 weeks' gestation and continued during pregnancy. During labor, a loading dose of 2 mg/kg AZT is administered intravenously, followed by continuous infusion of 1 mg/kg/h until delivery. The purpose of this study was to develop a rat model to study the disposition of AZT near term. The gestation period in rats is 21 to 23 days, thus, pregnant rats were administered AZT on day 20 of pregnancy.

Pregnancy is associated with numerous physiological alterations which may change during the course of pregnancy (11,12). These changes in physiological functions during pregnancy can, in turn, alter the pharmacokinetic characteristics of drugs (23,24). Pregnancy resulted in elevated plasma concentrations of AZT in both conscious and anesthetized rats near term. Renal clearance of AZT was decreased in pregnant rats. Similar pregnancy related decreases in renal clearance of drugs have been reported (23). AZT is renally excreted by glomerular filtration and active tubular secretion (16). Although renal plasma flow and glomerular filtration rate are increased during pregnancy (12), active tubular secretion has been reported to decrease (23). The results of this study indicate that the active tubular secretion mechanisms involved in the renal excretion of AZT is inhibited in the later stages of pregnancy. The decrease in CL_R, however, was not of great enough magnitude to affect total clearance of AZT.

No significant differences were noted in CL_T or CL_{NR} between female and pregnant rats. In general, the maternal drug metabolizing ability of rats is decreased in the later stages (19 - 20 days) of pregnancy (24), however, the metabolic reduction of the 3'-azido group of AZT appears to be unaffected by pregnancy. No differences were detected in V_{SS} values between pregnant and female rats. However, steady-state volume of distribution, normalized for body weight, was reduced in the pregnant rats compared to the female rats. The placenta, fetuses and amniotic fluid account for approximately 1.68%, 8.79% and 1.22% of the body weight in pregnant rats, respectively. However, the distribution of AZT into the rat fetuses and other pregnancy related spaces, appears to be minimal. Thus, the higher AZT concentrations in the pregnant rats can be largely attributed to the larger dose (mg) administered to the heavier pregnant rats.

Overall, there was no major effect of pregnancy on the pharmacokinetics of AZT in the rat. Similar lack of effects of pregnancy on AZT disposition have been reported for pregnant macaque monkeys (14) after intravenous administration of AZT and pregnant women (25) after oral administration. In contrast, a study by Watts *et al.* (6) suggests that the clearance and volume of distribution of AZT after oral drug administration are increased in women during pregnancy.

It is well known that many anesthetic agents change regional hemodynamics and drug disposition (17). Studies have shown that many anesthetic agents such as barbiturates are not suitable for cesearian section as they do not provide complete muscle relaxation at safe doses (26). In this investigation, rats were maintained under anesthesia by intramuscular administration of ketamine:acepromazine:xylazine at approximately 1.5 h intervals. This anesthetic dosage regimen was effective in maintaining complete anesthesia. This mixture of anesthetic agents is commonly used for surgical procedures and has been shown to be highly effective for long term anesthesia in laboratory animals (27,28).

Anesthesia using ketamine:acepromazine:xylazine produced marked changes in the disposition of AZT. Plasma concentrations of the nucleoside in the rats which were maintained under anesthesia were higher than those of the conscious animals. Significantly lower total, renal and non-renal clearances were noted in anesthetized rats, however, steady-state volume of distribution of AZT did not appear to be affected by anesthesia. The specific mechanisms by which anesthesia alters the elimination of AZT remains to be elucidated. However, the decreased clearance of AZT in anesthetized rats may be due to decreased renal and hepatic blood flow, decreased glomerular filtration, and hepatic enzyme inhibition caused by the anesthetic agents (17,29).

The removal of 2 pups by cesarian section at each sample time resulted in slightly elevated plasma AZT concentrations due to a decrease in renal clearance and steady-state volume of distribution. Mersatello (18) showed that surgery affected renal function by causing changes in renal hemodynamics. Blood loss during surgical procedures has also been shown to decrease renal blood flow (30). Hence, the decreased renal clearance of AZT when pups were removed by cesarian section is likely due to decreased renal blood flow. Since renal clearance was already decreased 5-fold by pregnancy and anesthesia, the further reduction in renal clearance due to the cesarian sections was not great enough to affect total clearance of the nucleoside. Similarly, the reduced volume of distribution in pregnant rats undergoing cesarian section was probably due to alterations in regional blood flow and blood loss.

In conclusion, with the exception of slightly reduced non-renal clearance in female rats, gender had no effect on the disposition of AZT in rats. Pregnancy resulted in a decreased renal clearance of AZT, however, total clearance, non-renal clearance and volume of distribution were not affected. Anesthesia caused a reduction in renal, non-renal total clearances of AZT. While there are limitations of the rat model, particularly the lack of a viral infected rat model, the rat appears to be a suitable laboratory animal model for in-

vestigating AZT disposition during pregnancy. However, results of pharmacokinetic studies when animals are maintained under anesthesia with ketamine:acepromazine:xylazine must be interpreted with caution.

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