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Pharmacokinetics of Nevirapine and Lamivudine in Patients with HIV-1 Infection

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ABSTRACT The purpose of this parallel treatment group, double-blind, multicenter study was to characterize the pharmacokinetics of nevirapine and lamivudine when coadministered to patients with the HIV-1 infection. This pharmacokinetic interaction study was nested within a larger Phase III clinical trial conducted to characterize the safety and efficacy of coadministered nevirapine and lamivudine. One hundred HIV-1 infected patients with CD4+ lymphocyte counts = 200 cells/mm^3 and who were on a background of nucleoside (zidovudine [ZDV], didanosine [ddI], zalcitabine [ddC], stavudine [d4T]) therapy were randomly assigned to be treated with either nucleoside + lamivudine + nevirapine or nucleoside + lamivudine + placebo. Each patient underwent blood sampling at defined times for the purpose of determining the concentration of nevirapine in plasma and lamivudine in serum under steady-state conditions. Each patient was also monitored closely for concomitant administration of other drugs, including ZDV, ddI, ddC, d4T and cotrimoxazole. The pharmacokinetics of nevirapine and lamivudine were characterized using nonlinear mixed-effects modeling. There were no reported serious adverse events during the 40-day pharmacokinetic study. The results of the modeling analysis revealed that nevirapine had no effect on the pharmacokinetics of lamivudine. Estimates of the apparent clearance for nevirapine (CL/F = 3.3 L/hour; 95% confidence interval [CI] 2.9 to 3.7 L/hour) and lamivudine (CL/F 27.6 L/hour; 95% CI 22 to 33.2 L/hour) were consistent with the values reported in earlier trials. However, the results also showed that concomitant administration of lamivudine with cotrimoxazole resulted in a 31% reduction in the apparent clearance of lamivudine, resulting in a 43% increase in the average steady-state lamivudine serum concentrations. These results indicate that chronic concurrent administration of cotrimoxazole with lamivudine may significantly affect the steady-state pharmacokinetics of lamivudine.

KEYWORDS: Nevirapine, Lamivudine, Drug Interaction, Enzyme Induction, Cotrimoxazole.

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INTRODUCTION An important objective in the clinical development of drugs is the identification of factors that may cause deviations from usually observed blood levels of a drug. Such factors pose a particularly acute problem in the treatment of the HIV infection because multiple combinations of drugs are often required to treat both the viral infection as well as the complications that arise from autoimmune dysfunction[1-3]. Nevirapine (Viramune®) and lamivudine (Epivir®) are 2 antiretroviral, reverse-transcriptase inhibitors that are currently approved for use in combination therapy to treat the HIV-1 infection.

The pharmacokinetics of nevirapine have been characterized in patients and healthy volunteers. Nevirapine is well absorbed orally (>90%), distributes well to nearly all tissues, and is approximately 60% bound to plasma proteins[4,5]. More than 80% of a nevirapine dose is biotransformed via P450 oxidation to hydroxylated metabolites that are subsequently largely excreted in urine as glucuronides[6]. Only a small fraction of the dose (<3%) is excreted unchanged in the urine. Treatment with 200 mg per day of nevirapine over a 2-week period results in P450 metabolic autoinduction of CYP3A and CYP2B6 pathways, as well as an increase in nevirapine apparent clearance and a decrease in nevirapine half-life from approximately 45 hours to 30 hours[6-9].

The pharmacokinetics of lamivudine (common name 3TC) have been well characterized[10-12]. Lamivudine is rapidly (>80%) absorbed orally and distributes to extravascular compartments. The drug is approximately 55% to 85% excreted in urine as unchanged drug and has a terminal-phase half-life of 3 hours. In vitro studies using cytochrome P450 (CYP) enzyme probes suggest that lamivudine has little potential to interact metabolically with other drugs, and few interaction studies of this type have been considered[12]. However, with the possibility of using these 2 drugs as part of a long-term combination therapy, the question of a pharmacokinetic interaction between lamivudine and nevirapine or lamivudine and one of nevirapine's urinary metabolites became a question of clinical importance. The objectives of the present study, which was part of a long-term efficacy trial to evaluate the effectiveness of nevirapine and lamivudine when added to a background of nucleoside therapy, were to determine the effects of nevirapine on the pharmacokinetics of lamivudine and to characterize the pharmacokinetics of nevirapine and lamivudine during coadministration to patients with the

HIV infection. As a secondary objective, given the size of the study population, the influence of other factors that might influence the pharmacokinetics of either drug, including patient demographics and concurrent administration of frequently administered drugs (eg, nucleosides and cotrimoxazole), was investigated.

MATERIALS AND METHODS

Study Design

The pharmacokinetic study was nested within a larger Phase III, double-blind, placebo-controlled, multicenter trial to evaluate the tolerance, safety, and effectiveness of nevirapine in preventing clinical AIDS progression events or death. Patients were randomized to receive either lamivudine + nevirapine or lamivudine + matching placebo on a stable background nucleoside therapy that consisted of zidovudine (AZT), didanosine (ddI), or zalcitabine (ddC). Protease inhibitors were not allowed. Furthermore, patients receiving acute therapy for AIDS-defining infections or malignancies were excluded from the study. Only patients who could receive the standard lamivudine dose of 150 mg twice a day (BID) were enrolled in the study. Lamivudine was administered as 150 mg BID and nevirapine as 200 mg daily for 2 weeks, then as 200 mg BID given concurrently with lamivudine. One hundred HIV-1 infected patients with $CD4^+$ cell counts = 200 cells/mm^3 (patient's lymphocyte activity assessment) and Karnofsky performance status scores = 70% (patient's daily activity assessment) were planned to be enrolled in the nested pharmacokinetic study. Background nucleoside therapy was closely monitored and was to be changed only in the event of continued intolerance to the nucleoside therapy, even at a reduced dose. In addition to nucleoside therapy, the majority of patients (~85%) enrolled in the trial were also being treated with cotrimoxazole (trimethoprim/sulfamethoxazole) at an average daily dose (160/800 mg) generally used to prevent pneumonia caused by *Pneumocystis carinii* [13].

The trial was conducted on an outpatient basis. A population pharmacokinetic approach to blood sampling and pharmacokinetic analysis was employed wherein 2 steady-state blood samples (one each for nevirapine and lamivudine) were taken from each patient at various specified times over a 12-hour dosing interval during a regularly scheduled outpatient visit at least 30 days after initiation of therapy. The pharmacokinetic study consisted of 6 patient groups according to their assigned clock time for sampling blood relative to the time of dosing. Two blood samples were obtained from each patient according to the following schedule: Group 1 (0 and 2 hours post dose, n = 20), Group 2 (1 and 3 hours post dose, n = 20), Group 3 (3 and 5 hours post dose, n = 20), Group 4 (5 and 7 hours post dose, n = 20), Group 5 (7 and 9 hours post dose, n = 10), and Group 6 (10 and 12 hours post dose, n = 10). The blood samples were obtained during a regularly scheduled outpatient visit. Patients were instructed by the investigator on the importance of taking their medications at the same time every day and were asked to return to the clinic at a designated time for blood sampling 1 month after initiation of combination therapy. During this outpatient visit, the time of the morning dose of lamivudine/nevirapine or lamivudine/placebo and the actual time of blood sampling were recorded in the case report form for each patient.

Bioanalytics

Two nevirapine plasma samples and 2 lamivudine serum samples were collected from each patient and stored at -20°C. Nevirapine concentrations were quantitated in plasma at Boehringer Ingelheim Pharmaceuticals (Ridgefield, CT) using a high-performance liquid chromatographic (HPLC) assay with ultraviolet (UV) detection[14]. The nevirapine assay limits of quantitation were 0.025 and 10 µg/mL. Lamivudine concentrations were quantitated in serum at PPD Pharmaco (Richmond, VA) using a validated HPLC assay with UV detection[11,12]. The limits of quantitation for the lamivudine assay were 0.005 and 5 µg/mL. Quality control samples for each compound had interday and intraday coefficients of variation consistently less than 15%.

Pharmacokinetic Model

The pharmacokinetics of lamivudine and nevirapine were characterized using nonlinear mixed-effects modeling with the population pharmacokinetics software package NONMEM (Version IV, Level 2)[15]. A one-compartment open model with first-order absorption and first-order elimination was evaluated as a structural model. Individual patient pharmacokinetic parameters and intersubject variability were estimated using an exponential error model according to the following equations:

$$K_{aj} = \theta_{Ka} \bullet \exp^{\eta Ka_j} \quad (1)$$

$$CL_j = \theta_{CL} \bullet \exp^{\eta CL_j} \quad (2)$$

$$V_{dj} = \theta_{Vd} \bullet \exp^{\eta Vd_j} \quad (3)$$

where K_{aj} is the first-order absorption rate constant, CL_j is the apparent clearance, V_{dj} is the apparent volume of distribution for the j^{th} subject, ? is the typical value or population mean estimate for the corresponding pharmacokinetic parameter, and ? is the interindividual variability associated with ?. Elimination half-life in plasma was derived from the relationship [ln(2) × Vd/CL]. For model building purposes, including evaluation of intercept terms, the following criteria were

used to evaluate goodness of fit: (a) minimization of the objective function (MOF), which was defined as minus the log likelihood of the data, (b) minimization of the standard errors for the parameter estimates (?), (c) randomness of scatter in appropriate plots, (d) minimization of interpatient variability (omega), and (e) minimization in residual variability (sigma).

Covariate testing was accomplished by adding continuous (body weight, age) and categorical (nevirapine, gender, con-meds) variables to the structural model to determine if their addition significantly improved the overall fit and reduced variability. Influential covariates were also identified using S-PLUS[16] with the Xpose[17] software package and the generalized additive modeling procedure implemented in that software. In this study, the effects of nevirapine coadministration on the pharmacokinetics of lamivudine were assessed in NONMEM using a binary coding system, which is expressed mathematically as the following equation:

$$\hat{CL} = \theta_{CL} \bullet (1 + (\chi \cdot \theta_{NVP})) \quad (4)$$

In this equation, when the categorical covariate ? represents nevirapine administration and has a value of zero (ie, lamivudine + placebo), only $?_{CL}$ remains. However, for individuals receiving both lamivudine and nevirapine (? = 1) the value of lamivudine clearance was adjusted slightly to reflect the contribution of the covariate to the model.

RESULTS

Patient Demographics

Of the 101 patients enrolled in the nested pharmacokinetic study, a total of 90 patients were included in the pharmacokinetic analysis; 11 patients were excluded because it was not possible to determine the exact time of blood sampling relative to the time of the previous dose. A total of 177 plasma nevirapine samples and serum lamivudine samples were used for the pharmacokinetic analysis. A frequency distribution of the plasma/serum samples relative to the elapsed time after dosing is shown in **Figure 1**.

Patient demographics for each treatment group are summarized in **Table 1** The mean age of the study population ranged from 24 to 59 years (mean ± SD, 39.3 ± 7.1 years), and the average $CD4^+$ cell count was 109 ± 79 cells/mm^3. Subjects' average weight was 77.7 ± 15.1 kg. There was no significant difference between the treatment groups with respect to gender, age, weight, $CD4^+$ cell count, or concomitant use of nucleosides. A total of 77 of the 90 patients with evaluable pharmacokinetic data were taking cotrimoxazole (trimethoprim/sulfamethoxazole) concurrently with lamivudine or lamivudine + nevirapine. Within that group, the cotrimoxzole dose was 160/800 mg once daily for 51

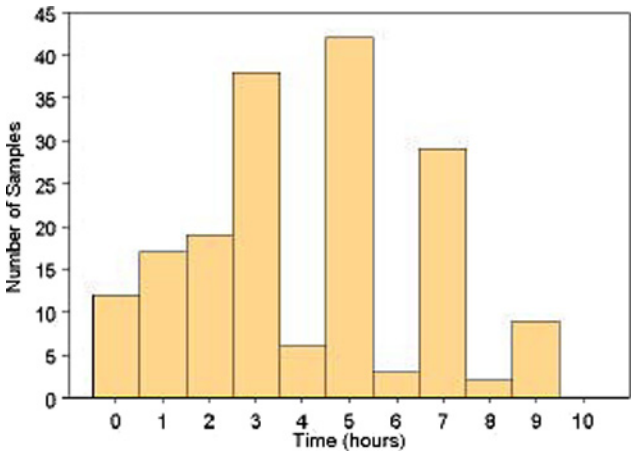

Figure 1. Frequency distribution of the elapsed time after dosing for 177 samples; the time values represent the midpoints of 1-hour intervals.

(66%) patients, 160/800 mg every other day or 3 times per week for 23 (30%) patients, and 160/800 mg twice daily for 3 (4%) patients.

There were no reported serious adverse events during the 40-day study period. Adverse effects, regardless of causality, included 17 reports associated with skin or appendages (including 5 reports of maculopapular rash, erythematous rash, or pruritis), nausea (11), fatigue (8), diarrhea (7), and headache (5). Overall, the treatments were well tolerated during the 40-day pharmacokinetic study.

Nevirapine Pharmacokinetics

The pharmacokinetics of nevirapine were evaluated by fitting a 1-compartment model with first-order absorption and elimination to the nevirapine plasma concentration-time data in the 43 patients who were treated with nevirapine. The nonlinear mixed effects modeling (NONMEM) structural model included an exponential error model to describe the intersubject variability and a constant coefficient of variation model to describe intrasubject variability. The study population's pharmacokinetic estimates are given in **Table 2** The values for nevirapine apparent clearance (CL/F = 3.3 L/hour; 95% CI 2.9 to 3.7 L/hour) and volume of distribution (V/F = 68.8 L; 95% CI 39.8 to 97.8) were consistent with the CL/F and V/F values from other studies in which P450 autoinduction was observed[4,6-9]. Nevirapine CL/F was not significantly affected by patient demographics (age, gender) or concomitant administration of cotrimoxazole and was only marginally affected by patient weight. A plot of the observed nevirapine plasma concentrations and a steady-state nevirapine concentration profile derived from the NONMEM parameters are shown in **Figure 2**.

Table 1.

Table 1. Patient Demographics

Patient Demographics	3TC + NVP	3TC + Placebo	Total
Gender			
Male	35	40	75
Female	8	7	15
N	43	47	90
Age (years)	38.2 ± 6.2	40.3 ± 7.8	39.3 ± 7.1
Body Weight (kg)	77.1 ± 14.0	78.3 ± 16.1	77.7 ± 15.1
CD4+ Cells (cells/mm^3)	105 ± 67	113 ± 88	109 ± 79
Con-meds			
TMP/SMX	34	35	77
ZDV	26	29	61
d4T	15	16	34
ddI	2	3	6
ddC	4	5	10

Table 2.

Table 2. Nevirapine Population Pharmacokinetic Estimates

Estimate	$\hat{ka}$ (h^{-1})	$\hat{CL}/F$ (L/hr)	$\hat{V}/F$ (L)
Estimate	1.1	3.3	68.8
SEE	0.2	0.2	14.8
95%CI	[0.7, 1.5]	[2.9, 3.7]	[39.8, 97.8]
Omega (%)	9.6%	23.1%	79.1%

Estimate = population average
SEE = standard error of the estimate
Omega (intersubject variability) = $[\sqrt{\omega^2}] * 100$
95%CI = 95% confidence interval = $[\theta \pm SEE \times 1.96]$

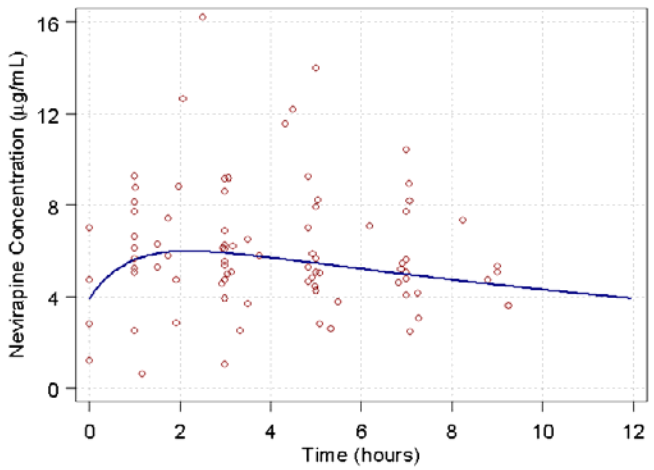

Figure 2. Observed concentrations of nevirapine (circles) and steady-state concentration profile.

Lamivudine Pharmacokinetics

The effects of nevirapine as well as concomitant administration of cotrimoxazole was evaluated using NONMEM analysis in all 90 HIV patients who were treated with lamivudine. A 1-compartment model with first-order absorption and elimination was determined to be the best pharmacokinetic model to describe the relationship of lamivudine serum to concentration time. The structural model was completed by describing intersubject variability with an exponential error model and intrasubject variability with a constant coefficient of variation model. The addition of a term for absorption lag time into the structural model resulted in unstable solutions with generally little effect on the overall MOF. The influence of nevirapine and several other covariates on the pharmacokinetics of lamivudine was evaluated by sequential addition of these variables to the NONMEM structural model to determine if their addition significantly improved the overall fit and reduced variability.

Scatterplots of the population and individual predicted lamivudine concentrations versus the measured lamivudine concentrations indicated that the model predicted the population lamivudine concentrations reasonably well, although there was a tendency to underpredict observed concentrations greater than about 2 µg/mL. Addition of a covariate term for coadministration with nevirapine resulted in no significant improvement in the structural model. Additionally, there was no observable difference in the post hoc estimates of lamivudine apparent clearance and half-life in the nevirapine-treated group when compared to the placebo group (**Figure 3**).

Of the covariates tested in the present study, lamivudine apparent clearance (CL/F) was not influenced by gender or race and was only marginally influenced by patient age and/or creatinine clearance. More important, there was no significant effect by nevirapine on lamivudine CL/F or V/F. The simulated lamivudine serum concentration time profiles and post hoc estimates of lamivudine CL/V in the presence and absence of nevirapine are illustrated in Figures **2** and **3**, respectively. Lamivudine clearance was significantly reduced (- 30.5%; 95% CI - 46% to - 15%) by coadministration with cotrimoxazole (**Table 3**). The final equation, which best described the apparent clearance of lamivudine in this study, was as follows:

$$\hat{C}L/F = \theta_{CL} \bullet (1 + \chi \bullet \theta_{CL}^{TMP}))$$

.....(5)

where "?" equals zero for no coadministered cotrimoxazole and one for coadministered cotrimoxazole, $?_{CL}$, and $?^{TMP}{}_{CL}$ are equivalent to the values reported in **Table 3**.

Discussion Although the potential for lamivudine to interact metabolically with other drugs has been considered to be low, this study confirms that a pharmacokinetic drug interaction does not exist between lamivudine and nevirapine, a drug that is known to induce P450 metabolic isozymes CYP3A4 and CYP2B6. The pharmacokinetics of nevirapine were consistent with that of several earlier trials[5,6,8, 19]. Therefore, the 2 drugs can be administered concurrently to HIV-1 - infected patients without regard to dosage adjustment for either drug.

Of all the possible covariates that might affect the pharmacokinetics of nevirapine or lamivudine, only cotrimoxazole was found to significantly affect the pharmacokinetics of lamivudine. Other covariates, such as creatinine clearance or age, were marginally influential in predicting the pharmacokinetics of lamivudine, but not nevirapine. The effect of age, however, which ranged from 25 to 60 years, may be at least in part explained by the decline in creatinine clearance with advancing age. The 90 patients included in the pharmacokinetic analysis generally had normal renal function for their age, and no trends with respect to changing renal or hepatic function were observed during the 40-day concomitant treatment period. Coadministration with ZDV, d4T, ddI, or ddC was not associated with a change in the pharmacokinetics of either nevirapine or lamivudine. The absence of serious adverse events suggests that the combination of nevirapine with lamivudine was well tolerated during the 40-day pharmacokinetic trial. However, the long-term safety and tolerance of this combination will be presented elsewhere.

The results of the mixed-effects pharmacokinetic modeling showed that chronic concomitant administration of lamivudine with cotrimoxazole resulted

Table 3.

Table 3. Lamivudine Population Pharmacokinetic Estimates

Pharmacokinetic Estimate	$\hat{CL}/F$ (L/hr) θ_{CL}	θ_{CL}^{TMP}	$\hat{V}/F$ (L)
Estimate	27.6	- 0.305	86.5
SEE	2.86	0.08	8.58
95%CI	[22.0, 33.2]	[- 0.46, - 0.15]	[69.7, 103.3]
Omega (%CV)	18%		7%

$$\hat{CL}/F = \theta_{CL} \bullet (1 + (\chi \bullet \theta_{CL}^{TMP}))$$

θ = parameter of interest
SEE = standard error of the estimate
Omega (intersubject variability) = $[\sqrt{\omega^2}] * 100$
95%CI = 95% confidence interval = $[\theta \pm SEE \times 1.96]$

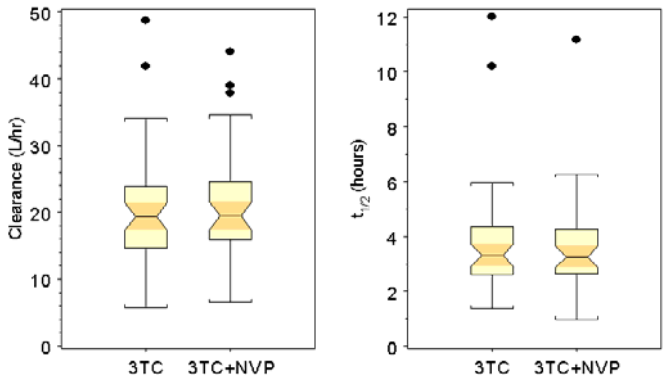

Figure 3. Post hoc estimates of lamivudine's (3TC) apparent clearance and half-life. The bottom and top of each box represent the 25th and 75th percentiles, with the median drawn at the center of the notched area. The vertical lines extend to 1.5 interquartile ranges. Values more extreme are outliers and are marked by closed circles. The notched area above and below the median mark the confidence intervals.

in a significant 31% reduction in apparent oral clearance of lamivudine in the 77 patients who took the 2 drugs concurrently in this study. The drug interaction of this magnitude can be expected to result in an approximately 43% increase in the average steady-state concentration of lamivudine when the 2 drugs are taken concurrently (**Figure 4**). The cotrimoxazole dose used in two thirds of the cotrimoxazole-treated patients in this study and the resultant drug interaction between cotrimoxazole and lamivudine are consistent with the previously reported results of a study in which a single 300-mg dose of lamivudine was administered before and after a 5-day course of cotrimoxazole 160/800 mg/day[11]. In that study, a 43% increase in the lamivudine area under the concentration-time curve was observed, as well as a 35% reduction in the lamivudine renal clearance (CL_R). The results of the present study also agree with published data regarding the effects of sulfamethoxazole and trimethoprim on the renal disposition of lamivudine in the isolated rat kidney perfusion model[18]. In this system, trimethoprim reduced the renal clearance of lamivudine by 59%, presumably by competitive inhibition of tubular secretion by trimethoprim in a concentration-dependent manner.

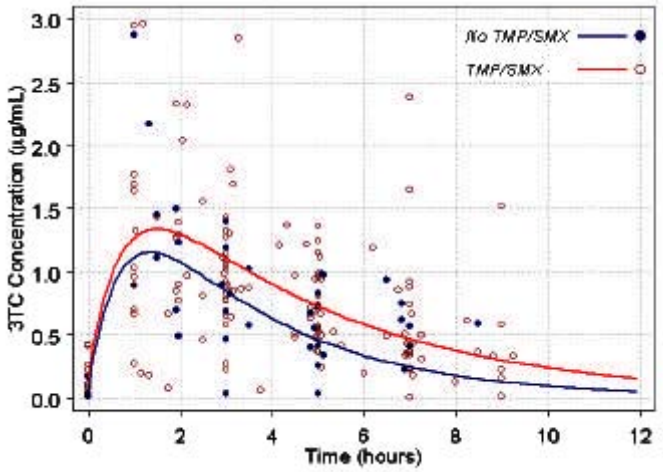

Figure 4. Lamivudine (3TC) serum concentrations in the absence (blue line, closed circles) and presence (red line, open circles) of cotrimoxazole (TMP/SMX).

CONCLUSION Overall, this study showed that a pharmacokinetic drug interaction did not exist between nevirapine, an inducer of P450 metabolism, and lamivudine when the 2 drugs were administered concurrently as part of triple-combination therapy that included 5a nucleoside. The presence of a cotrimoxazole effect with chronic administration of lamivudine with cotrimoxazole was consistent with the previously reported effects of cotrimoxazole on the single-dose pharmacokinetics of lamivudine.

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REFERENCES

1. Piscitelli SC, Flexner C, Minor JR, Polis MA. Drug interactions in patients with human immunodeficiency virus. Clin Inf Dis. 1996;23:685-693.

2. Barry M, Mulchahy F, Merry, Gibbons S, Back D. Pharmacokinetics and potential interactions amongst antiretroviral agents used to treat patients with HIV infection. Clin Pharmacokin. 1999;36:289-304.

3. Bertz RJ, Granneman GR. Use of in vitro and in vivo data to estimate the likelihood of metabolic pharmacokinetics interactions. Clin Pharmacokin. 1997;32:210-258.

4. Murphy RL, Montaner J. Nevirapine: a review of its development, pharmacological profile and potential for clinical use. Exp Opin Invest Drugs. 1996;5:1183-1199.

5. Lamson MJ, Cort S, Sabo JP, Keirns JJ. Assessment of nevirapine oral bioavailability in healthy volunteers following oral and intravenous administration. Pharm Res. 1995;12:S-415.

6. Riska PR, Lamson MJ, MacGregor TR, et al. Disposition and biotransformation of the antiretroviral drug nevirapine in humans. Drug Metab Disp. 1999;27:895-901.

7. Havlir D, Cheeseman SH, McLaughlin MM, et al. High-dose nevirapine: safety, pharmacokinetics, and antiviral effect in patients with human immunodeficiency virus infection. J Inf Dis. 1995;171:537-545.

8. Lamson MJ, Cort S, Sabo JP, MacGregor TR, Keirns JJ. Effects of gender on the single and multiple dose pharmacokinetics of nevirapine. Pharm Res. 1995;12:S-101.

9. Murphy R, Sommadossi JP, Lamson MJ, Hall DB, Myers MM, Dusek A. Antiviral effect and pharmacokinetic interaction between nevirapine and indinavir in HIV-1 infected individuals. J Inf Dis. 1999;179:1116-1123.

10. Van Leeuwen R, Lange JMA, Hussey EK, Donn KH, Hall ST, Harker AJ. The safety and pharmacokinetics of a reverse transcriptase inhibitor, 3TC, in patients with HIV infection: a phase I study. AIDS 1992;6:1471-1475.

11. Moore KHP, Yuen GJ, Raasch RH, Eron JJ, et al. Pharmacokinetics of lamivudine administered alone and with trimethoprim-sulfamethoxazole. Clin Pharm Ther. 1996;59:550-558.

12. Johnson MA, Moore KHP, Yuen GJ, Bye A, Pakes GE. Clinical pharmacokinetics of lamivudine. Clin Pharmacokin. 1999;36:41-66.

13. Eron JJ, Benoit SL, Jemsek J, et al. Treatment with lamivudine, zidovudine, or both in HIV-positive patients with 200 to 500 CD4+ cells per cubic millimeter. N Engl J Med. 1995;333:1662-1669.

14. Pav JW, Rowland LS, Korpalski DJ. HPLC-UV method for quantitation of nevirapine in biological matrices following solid-phase extraction. J Pharm Biomed Anal. 1999;20:91-98.

15. Beal SL, Sheiner LB. NONMEM Users Guide, Parts I-VI, Division of Clinical Pharmacology, NONMEM Project Group, University of California at San Francisco, San Francisco, CA, 1979-1992.

16. Jonsson EN, Karlsson MO. Xpose - An S-PLUS based population pharmacokinetic/pharmacodynamic model building aid for NONMEM. Comput Methods Programs Biomed. 1999;58:51.

17. S-PLUS Version 4.5. Data Analysis Products Division, MathSoft, Seattle, WA.

18. Sweeney KR, Hsyu P-H, Statkevick P. Renal disposition and drug interaction screening of (-)-2'-deoxy-3'-thiacytidine (3TC) in the isolated perfused rat kidney. Pharm Res. 1995;12:1958-1963.

19. Lamson MJ, Sabo JP, MacGregor TR, Pav JW, Rowland L, Hawi A, et al. Single dose pharmacokinetics and bioavailability of nevirapine in healthy volunteers. Biopharm Drug Disposition. 1999;20:285-291.