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Pharmacokinetics of Nevirapine: Initial Single-Rising-Dose Study in Humans

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Nevirapine, a nonnucleoside inhibitor of human immunodeficiency virus type 1 (HIV-1) reverse transcriptase, was administered for the first time to humans in a pilot study designed to investigate the pharmacokinetics and tolerance of the drug following single-dose administration to 21 HIV-1-infected individuals. The study followed a parallel design. Different groups of three subjects each were given one of seven dose levels (2.5 to 400 mg) in sequential order, starting with the lowest dose. Each subject received only one dose. Nevirapine was rapidly absorbed at all doses from a tablet formulation. Peak concentrations in plasma were generally achieved within 90 min of dose administration. Secondary peaks were also noted between 3 and 12 h or between 24 and 28 h, the latter being noted mainly in subjects receiving the higher doses. After 24 h, concentrations in plasma declined in a log-linear fashion. The terminal half-life and mean residence time exceeded 24 h in all but one subject, indicating a prolonged disposition time in this population. Both peak concentrations in plasma and areas under the plasma concentration-time curves increased proportionally with increasing dose from 2.5 to 200 mg; however, the increase in the peak concentration in plasma and the area under the plasma concentration-time curve appeared to be less than proportional at the 400-mg dose level in this small number of subjects. This observation may be due to increased clearance or decreased absorption at the highest dose or population differences in absorption or clearance between doses. Studies with a cross-over design are planned to resolve these issues. The pharmacokinetic characteristics of nevirapine are appropriate for once-daily administration. A daily 12.5-mg dose is predicted to achieve trough concentrations in plasma in the range required to totally inhibit replication of wild-type HIV-1 in human T-cell culture.

Nevirapine, formerly known as BI-RG-587, is a potent nonnucleoside reverse transcriptase inhibitor specific for human immunodeficiency virus type 1 (HIV-1) (7) which shows good characteristics for development as a potential therapeutic agent. The 50% inhibitory concentration (IC_{50}) in human T-cell culture is 10.6 mg/ml (40 nM) and the therapeutic index is 8,000 (6). Nevirapine in combination with zidovudine exhibits synergistic antiviral activity without increased cytotoxicity (11). The structure of nevirapine is shown in Fig. 1. It is a low-molecular-weight compound which is lipophilic (partition coefficient = 83) and a weak base (pK_a = 2.8). It is highly soluble at pH <3, but its aqueous solubility decreases to approximately 0.1 mg/ml at neutral pH.

Studies in chimpanzees demonstrated high bioavailability (64%) and a long half-life ($t_{1/2}$; 11 to 24 h) (4), and studies in rats indicated even distribution throughout the body, including the brain (8). The plasma:cerebrospinal fluid distribution ratio in two cynomolgus monkeys 2 h after oral administration of 20 mg/kg of body weight was 0.4; in these same animals plasma:brain distribution ratios were 0.8 and 1.4, respectively. In vitro protein binding studies with rat and human plasma showed that plasma protein binding was 51 and 62%, respectively. In vitro metabolism experiments with liver microsomes from humans, rats, monkeys, and dogs showed hydroxylation at several sites, the major oxidative metabolite being hydroxymethyl-nevirapine. In chimpanzee, rat, and dog, the urinary excretion of parent drug was low, suggesting liver metabolism as the major route of clearance. Induction of cytochrome P-450 2B1 (phenobarbital-inducible) and 3A (alcohol-inducible) isozymes occurred in rats after repeated dosing at 10 mg/kg and higher (2). However, short-term safety studies in rats and dogs showed no toxicities which would preclude development of the compound.

The objectives of the present study were to generate initial information on nevirapine pharmacokinetics and dose proportionality and to assess the safety and tolerance of single rising doses in subjects with HIV-1 infection. These data could then be used to determine initial dose, schedule, and a dose escalation scheme for a multiple-dose clinical study of nevirapine. For ethical reasons, our goal for the multiple-dose trial was to achieve concentrations in plasma even at the lowest dose levels which could be expected to provide complete inhibition of reverse transcriptase on the basis of cell culture data.

A few months after this single-dose study was completed and after initiation of multiple-dose trials, results of cell culture experiments which showed rapid development of resistance to nonnucleoside reverse transcriptase inhibitors, including nevirapine, were reported (9, 12, 13). This phenomenon was confirmed in the initial clinical trials in HIV-1-infected persons treated with these compounds (10). Nevirapine inhibits the most common mutant reverse transcriptase enzyme (Tyr-181 to Cys) with an IC_{50} of 700 ng/ml (2.6 μM), compared with an IC_{50} of 10.6 ng/ml (0.04

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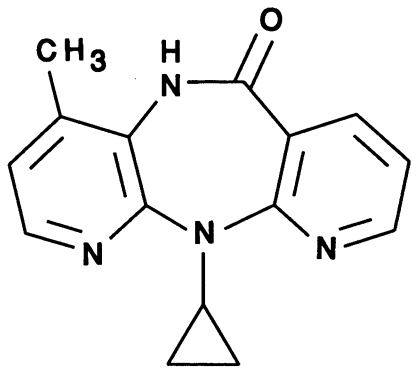


FIG. 1. Nevirapine, 5,11-dihydro-11-cyclopropyl-4-methyl-6H-dipyrido-[3,2-b2',3'e][1,4]diazepin-6-one (molecular weight, 266.302).

μM) for the wild-type enzyme. As a result of these observations, clinical studies have been redesigned to target higher concentrations of nevirapine in plasma in the hopes of inhibiting variant virus with reduced susceptibility to the compound.

MATERIALS AND METHODS

The participants were HIV-1-infected persons with absolute CD4 counts of <400/μl. The volunteers were 18 men and 3 women ranging in age from 19 to 46 years. Six volunteers had AIDS, and 10 had AIDS-related complex; their CD4 counts ranged from 0 to 379 (mean ± standard deviation, 191 ± 124). By transmission category, there were 12 homosexual males, 2 homosexual males who also used intravenous drugs, and 7 intravenous drug users. Three individuals were Latino and one was African-American. The University of Massachusetts Medical School Human Subjects Committee reviewed and approved the study and the document which all participants signed to provide informed consent.

Three persons receiving each dose level were studied simultaneously. Doses were 2.5, 12.5, 25, 50, 100, 200, and 400 mg given as tablets containing 2.5, 12.5, or 50 mg of nevirapine. Table 1 shows the doses achieved in terms of milligrams per kilogram for individuals in each cohort. Concomitant medications were kept to a minimum, and drugs with known interactions with phenobarbital were required to be stopped 28 days prior to the trial, as were any investigational agents. Zidovudine was continued until 7 days before the trial and was resumed upon its completion. A urine specimen for drug screening was collected at the time of admission to hospital for the study. Participants fasted overnight under observation and received a single dose of nevirapine after initial blood sampling the following morning.

Blood for determination of nevirapine levels in plasma was drawn at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 28, and 32 h after dosing. An electrocardiograph was obtained at 2 h postdosing. Volunteers were discharged from the hospital after the 32-h blood draw. Blood for repeat determination of nevirapine levels in plasma were drawn at 48 and 72 h, since preclinical studies suggested a complete plasma nevirapine concentration-time curve could be obtained within this time frame. After administration of the 12.5-mg dose, it became apparent that nevirapine clearance in humans was lower than that predicted from studies in animals, so additional plasma samples were collected at 96 h and between 168 and 200 h when possible.

Plasma was separated promptly, stored at −80°C, and assayed by high-pressure liquid chromatography (HPLC) after inactivating the virus by heating at 56°C for 30 min. The assay was validated for precision and accuracy and is linear from 25 to 10,000 ng/ml (5). Extraction recovery was greater than 88% of the spiked amounts at all concentrations for both nevirapine and the internal standard. Extracted drug-free human plasma samples demonstrated the absence of any interfering or coeluting components. A total of 25 standard curves were used during analysis of the study samples. The coefficient of variation of the slopes of the curves as determined from unweighted linear regression was 3.4%. Six different concentrations of quality control standards run during the study had intraday and interday relative standard deviations ranging from 4.6 to 12.4%, and the deviation from the nominal value was 9.7% or less. The limit of quantitation, defined as the lowest standard with a relative standard deviation of <15%, was 25 ng/ml.

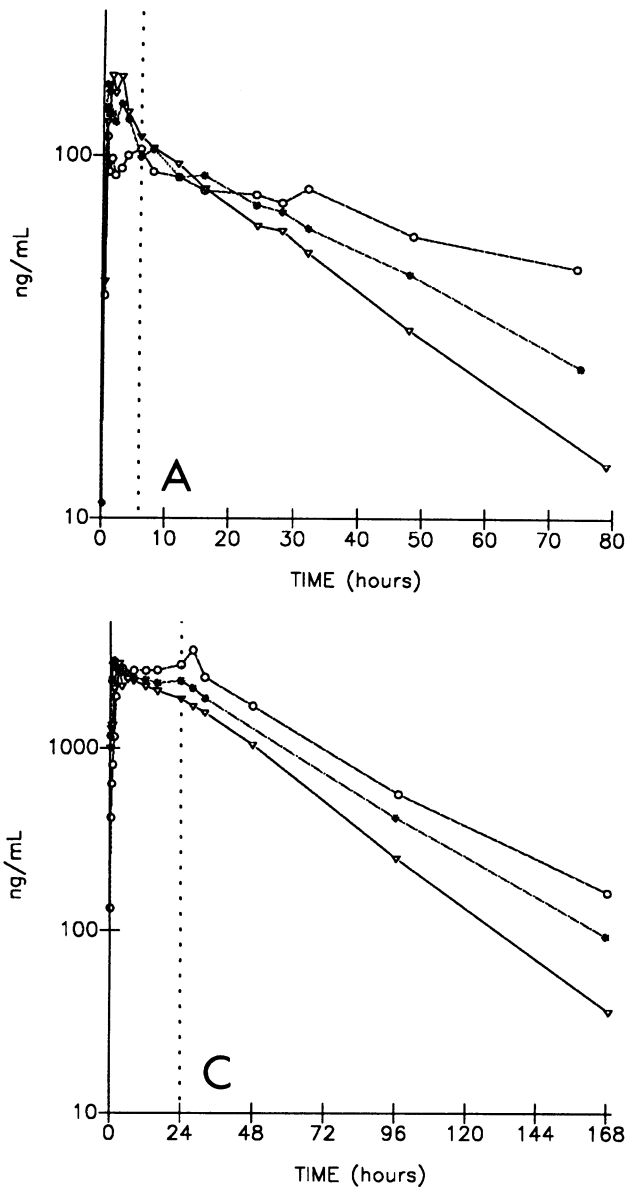
The area under the plasma concentration-time curve (AUC) was calculated by the linear trapezoidal rule method. The relationships of AUC and the peak concentration of nevirapine in plasma (C_{max}) with dose were examined by linear and quadratic least-squares regression of the AUC or C_{max} data versus dose. The quadratic term was required to be statistically significant at the 0.05 level to be accepted as evidence of deviation from linearity.

Apparent oral clearance was estimated from the ratio of the dose administered to the observed AUC. The apparent volume of distribution at steady state was calculated from the ratio of dose-adjusted area under the moment curve to AUC. $t_{1/2}$ was estimated by linear regression of log plasma nevirapine concentration-versus-time data. The datum points included in the regression analysis of the terminal elimination phase were determined from visual inspection of graphic semilogarithmic plots of the data. Steady-state plasma nevirapine concentrations, assuming once-daily dosing, were calculated for each individual from the ratio of AUC to the dosing interval. Trough concentrations predicted to be achieved at steady state were estimated from the individual average steady-state concentrations, individual $t_{1/2}$s, and the dosing interval chosen for initial multiple-dose studies (24 h) (3).

RESULTS

Pharmacokinetics. Individual semilogarithmic plots of plasma nevirapine concentration-time course data after administration of single doses of 12.5, 200, and 400 mg of nevirapine are shown in Fig. 2A to C, respectively. The first time point used in the linear regression for calculation of the $t_{1/2}$ for each individual is shown by the dashed line. For the majority of the subjects, six or nine datum points were included in the regression analysis. Only four datum points were available for estimation of the $t_{1/2}$ of nevirapine in subject 16 (200-mg dose level). All subjects had detectable levels of nevirapine in plasma after administration of the lowest (2.5-mg) dose, but the majority of the concentrations were below the linear range of the assay, precluding further pharmacokinetic analysis. Concentrations in the plasma of all other subjects at all time points in the study were above the limit of quantitation of the assay.

Noncompartmental pharmacokinetic parameters are listed for individual subjects in Table 1. The drug was rapidly absorbed; substantial amounts of nevirapine were present in the systemic circulation as early as 15 min after the tablets were ingested. The time-concentration profiles observed



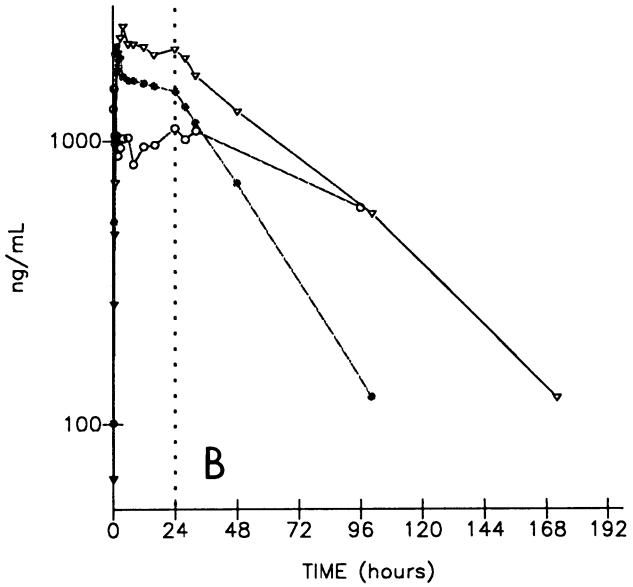


FIG. 2. Plasma nevirapine concentration-time courses after administration of 12.5-mg (A), 200-mg (B), and 400-mg (C) single doses in HIV-1-infected volunteers. The dashed lines are placed at the first time points used in the linear regression analysis for calculation of $t_{1/2}$. Drug concentrations were determined by a validated HPLC method which was linear from 25 to 10,000 ng/ml.

were characterized by an initial early concentration peak occurring at a mean of 2.2 h (0.5 to 6 h) after dose administration; this was followed by a concentration plateau which concluded in a secondary concentration maximum at a mean of 14 h in many subjects. There was a bimodal distribution of secondary maxima which occurred either between 3 and 12 h or between 24 and 28 h. The secondary maximum tended to occur during the later time frame at the higher dose levels. Visual inspection of semilogarithmic plots of the concentration-versus-time data revealed that, in most subjects, the concentration plateau extended to approximately 24 h, after which time nevirapine concentrations declined in a log-linear fashion.

AUC and C_{max} increased with increasing dose. It should be noted that, in some cases, a large portion of the AUC (and mean residence time) was extrapolated because of the lack of samples obtained at later time points. Greater than 20% of the calculated AUCs were extrapolated for two of three subjects in the 25- and 50-mg dose cohorts; however, in the 12.5-, 100-, 200-, and 400-mg dose cohorts, substantial extrapolation occurred in calculating the AUC for only one of three subjects at most. Figure 3A illustrates the relationship between AUC and dose. The AUC increased proportionally with respect to dose over the dosing range of 12.5 to 100 mg. At higher doses there appeared to be deviation from linearity, especially in the 200- to 400-mg dosage increment, in which a 2-fold increase in dose resulted in only a 1.2-fold increase in the AUC. Regression analysis showed that both linear and quadratic terms were statistically significant in modeling the AUC-dose relationship ($P < 0.001$ and $P < 0.01$, respectively). For the quadratic fit, the parameter estimate for the linear term was 0.994 (standard error [SE] = 0.096), the estimate for the quadratic term was −0.00145 (SE = 0.000269), and the adjusted r^2 was 0.952 for a no-intercept model. For the linear fit, the parameter estimate was 0.498 (SE = 0.045), and the adjusted r^2 was 0.873 for a no-intercept model. The no-intercept model was used because predose concentrations in plasma were less than the limit of quantitation. Figure 3B shows the relationship between C_{max} and dose. As with AUC, both the linear and the quadratic terms were statistically significant ($P < 0.001$ and $P < 0.05$, respectively). For the quadratic fit, the parameter estimate for the linear term was 0.013 (SE = 0.001), the estimate for the quadratic term was −0.0000139 (SE = 0.0000033), and the adjusted r^2 was 0.973 for a no-intercept model. For the linear fit, the parameter estimate was 0.0085 (SE = 0.00047) and the adjusted r^2 was 0.947 for a no-intercept model.

Mean apparent oral clearance was 0.39 ml/kg/min in this small population of subjects. The $t_{1/2}$ ranged from 22 to 84 h, with a harmonic mean of 40 h. Mean residence time averaged 69 h. The mean apparent volume of distribution was 1.37 liters/kg.

Adverse events. No serious adverse events occurred. Two subjects at the 2.5-mg dose and one subject each at the 12.5-,

TABLE 1. Individual noncompartmental pharmacokinetic parameters after single doses of nevirapine in HIV-1-infected subjects[a]

Dose (mg) and subject no. (dosage [mg/kg])	$AUC_{0-\infty}$ (μg · hr/ml)	C_{max} (ng/ml)	T_{max} (h)	$t_{1/2}$ (h)	MRT (h)	CL_p/F (ml/kg min^{-1})	V_{ss}/F (liters/kg)
2.5							
1 (0.03)		<25					
2 (0.03)		40					
3 (0.04)		30					
12.5							
4 (0.17)	10.23	113	0.75	77	103	0.30	1.86
5 (0.18)	6.04	157	0.75	35	49	0.48	1.41
6 (0.18)	4.71	166	1.5	24	34	0.63	1.31
25							
7 (0.38)	27.34	325	0.50	51	80	0.23	1.13
8 (0.48)	14.56	589	0.50	28	40	0.55	1.33
9 (0.49)	40.02	334	4	84	125	0.20	1.54
50							
10 (0.63)	46.20	646	1	54	73	0.30	1.33
11 (0.77)	63.82	584	6	73	100	0.20	1.21
12 (0.84)	29.78	451	4	44	67	0.35	1.42
100							
13 (1.39)	98.33	1,021	3	60	89	0.24	1.27
14 (1.39)	89.76	910	8	58	82	0.26	1.27
15 (1.62)	86.45	1,714	0.5	44	62	0.31	1.16
200							
16 (2.05)	150.53	1,534	0.5	70	113	0.23	1.54
17 (3.93)	89.01	2,148	1.5	22	34	0.77	1.57
18 (4.13)	167.06	2,529	4	37	56	0.39	1.30
400							
19 (4.89)	204.56	3,385	28	34	52	0.43	1.35
20 (4.92)	168.85	2,952	1.5	31	48	0.49	1.25
21 (5.33)	127.44	2,868	3	25	38	0.64	1.49

[a] $AUC_{0-\infty}$, area under the plasma nevirapine concentration-versus-time curve from time zero to infinity; C_{max}, maximum concentration in plasma; T_{max}, time to maximum concentration in plasma; $t_{1/2}$, half-life; MRT, mean residence time; CL_p/F, apparent oral clearance; V_{ss}/F, apparent volume of distribution at steady state.

200-, and 400-mg doses had headaches, all of which were mild. One person was noted to sleep during the day after the 200-mg dose but denied subjective somnolence, and no sedative effect was seen in any of the three recipients of the highest dose (400 mg). Two persons had gastrointestinal disturbances after the 12.5-mg dose; one of these individual's family members were also suffering similar symptoms. A single subject had tachycardia and confusion 6 to 16 min after ingestion of the 2.5-mg dose and subsequently complained of fatigue, irritability, and headache.

In summary, there was no dose-response relationship with any adverse event, and none were judged as probably or definitely caused by the drug. In comparison with pretreatment values, there were no meaningful changes in routine clinical laboratory test results obtained at 96 or 168 h postdosing (Table 2).

DISCUSSION

This report describes the first administration of nevirapine to humans. Nevirapine in single doses up to 400 mg by mouth was well tolerated. Peak concentrations in plasma exceeded the IC_{50} of nevirapine for the wild-type reverse transcriptase enzyme at all doses tested and for the Tyr-181 to Cys mutant at the three highest doses (100, 200, and 400 mg).

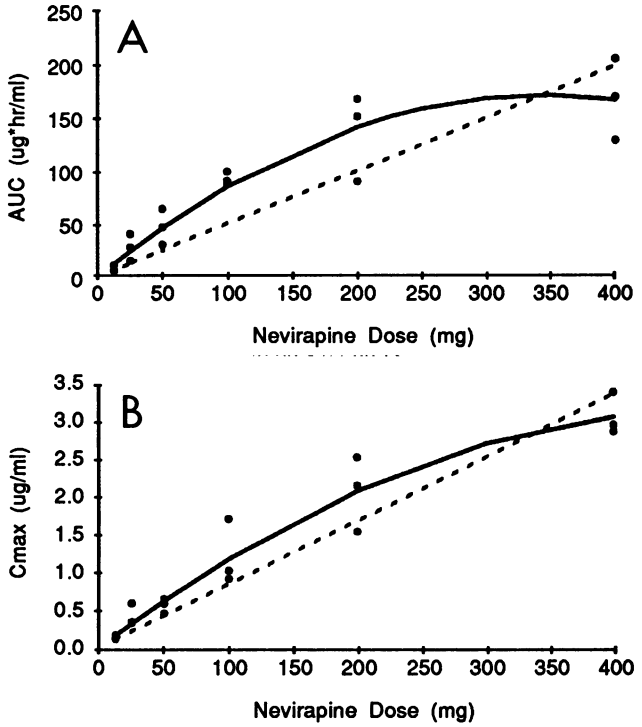


FIG. 3. (A) Area under the plasma nevirapine concentration-time curve as a function of weight-adjusted dose, showing least-squares linear and quadratic regression lines. (B) Nevirapine C_{max} as a function of dose, showing least-squares linear and quadratic regression lines. ●, observed; – – –, predicted, linear; ——, predicted, quadratic.

The profiles of the plasma nevirapine concentration-versus-time curves demonstrated a plateau at approximately 80% of the peak concentration that lasted about 24 h. This profile was not observed in animal pharmacokinetic studies, but it may be explained by enterohepatic recycling, as occurs in rats (8) and as suggested by the presence of a secondary concentration maximum. Alternatively, the rates of absorption and elimination over this period may be similar, thus balancing each other out. The first possibility can be excluded if the plateau does not occur following

TABLE 2. Laboratory tests

Test (units)	Mean ± SD	
	Predose	96–168 h postdose
Leukocyte (cells/mm^3)	4,400 ± 2,100	4,600 ± 1,800
Hemoglobin (g/dl)	13.30 ± 1.70	13.40 ± 1.70
Platelet count ($10^3/mm^3$)	220.8 ± 58.3	207.6 ± 66.30
Serum creatinine (mg/dl)	0.9 ± 0.2	0.9 ± 0.2
Alanine aminotransferase (U/liter)	43.4 ± 32.9	42.5 ± 31.4
Bilirubin (mg/dl)	0.6 ± 0.4	0.7 ± 0.5
Alkaline phosphatase (U/liter)	76.3 ± 14.3	76.3 ± 13.7

intravenous administration of nevirapine, but these data are not yet available.

The failure of the AUC to increase proportionately from the 200- to 400-mg dose may simply be a result of the small number of subjects and their variable health status, but it also raises the question of saturation of absorption or enhanced clearance at higher doses. Calculation of absorption potential at the various dose levels by the method of Dressman et al. (1) predicts decreased absorption at the 400-mg dose compared with that at the lower doses. Support for the possibility of enhanced clearance comes from the rapid induction of cytochrome P-450 2B1 observed in rats chronically dosed with nevirapine (2). The maintenance of relatively high concentrations in plasma during the plateau phase could result in hepatic enzyme induction at the highest dose even during the course of a single-dose study.

It is clear that nonlinear Michaelis-Menten kinetics do not occur when single oral 12.5- to 400-mg doses of nevirapine are administered, since Michaelis-Menten kinetics would lead to an upward rather than a downward curvature of the AUC-versus-dose plot. The dose linearity of nevirapine will be studied in detail by using larger numbers of subjects and steady-state dosing in a future trial.

The apparent volume of distribution calculated in humans is consistent with the values observed in rats, dogs, monkeys, and chimpanzees. It is also consistent with fairly even distribution throughout all organs and tissues within the body. Observed apparent oral clearance, $t_{1/2}$ (mean, >24 h), and mean residence time are similar to values obtained in chimpanzees (4) but not other species.

One of the objectives of the trial described here was to provide information for planning dosing levels and regimens for a rising-multiple-dose tolerance, pharmacokinetic, and activity study. In a chronic-dosing trial of nevirapine, we would hope to achieve trough concentrations in plasma of approximately 25 times the IC_{50} in human T-cell culture (40 nM) (6) using a dosing interval which would facilitate compliance. Therefore, predicted accumulation to average and trough steady-state nevirapine concentrations were calculated for once-daily dosing assuming linear accumulation (3) and the individual $t_{1/2}$s observed in the present study. A daily dose of 12.5 mg was predicted to produce trough concentrations in plasma at steady state of 13 to 36 times the IC_{50} and was chosen for the initial dose level. A fourfold dose escalation scheme, i.e., 50 and 200 mg, in succeeding cohorts should achieve trough levels in plasma of approximately 100 to 225 and 250 to 540 times the IC_{50}, respectively. The accuracy of these predictions and the ability to maintain the desired levels in plasma will be assessed in multiple-dose studies.

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