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Pharmacokinetics of GLQ223 in Rats, Monkeys, and Patients with AIDS or AIDS-Related Complex

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The pharmacokinetics of GLQ223 administered as a single short intravenous infusion to rats, monkeys, and patients with AIDS or AIDS-related complex (ARC) are presented. GLQ223 was given at a dose of 3,500 μg/kg of body weight to five Sprague-Dawley rats; a dose of 300 μg/kg was given to three cynomolgus monkeys; and doses of 1, 8, 16, 24, and 36 μg/kg were given to 10 patients with AIDS and 8 patients with ARC in an escalating dose design. Plasma clearance was 0.85 ± 0.24 liter/h/kg in rats, 0.16 ± 0.08 liter/h/kg in monkeys, and 0.13 ± 0.07 liter/h/kg in patients with AIDS or ARC. The volume of distribution at steady state was 0.42 ± 0.12, 0.21 ± 0.20, and 0.18 ± 0.50 liter/kg in rats, monkeys, and patients, respectively. The elimination half-life was 1.3 ± 0.4, 3.7 ± 1.5, and 3.2 ± 1.0 h in rats, monkeys, and patients, respectively. The disposition of GLQ223 was not dose dependent within the dose range tested in patients with AIDS or ARC. Interspecies pharmacokinetic scaling resulted in a good linear correlation for plasma clearance and the volume of distribution at steady state plotted versus species body weight on a log-log scale, indicating the predictability of elimination and distribution of GLQ223 among species. Allometric equations derived may be useful for the prediction of doses and dosage regimens to be used in animal models.

GLQ223 is a highly purified, formulated form of trichosantin, a 27-KDa basic protein isolated from the root tubers of *Trichosantes kirilowii* (13, 14). Recently, GLQ223 has been shown to have concentration-dependent anti-human immunodeficiency virus (HIV) activity manifested as a decrease in viral protein levels in acutely and chronically in vitro-infected cells of lymphocyte and mononuclear phagocyte lineage. Furthermore, a single, pulsed 3-h exposure of whole blood from HIV-seropositive patients to GLQ223 inhibited HIV antigen expression by monocytes or macrophages as measured by flow cytometry after 5 days of in vitro culture following treatment. Inhibition of HIV antigen expression persisted for up to 4 weeks, while the viability of HIV-infected monocytes was selectively reduced and no reduction was observed in GLQ223-treated uninfected cells (8).

Thus, GLQ223 is an interesting drug for the possible treatment of AIDS because of its unique activity on HIV-infected macrophages, manifested as a reduction in HIV antigen expression with apparent selective killing of infected cells, and its activity on infected lymphocytes. The aim of this paper is to describe GLQ223 pharmacokinetics obtained from preclinical studies in rats and monkeys as well as human pharmacokinetic data obtained from an escalating-dose, phase I, clinical trial in patients with AIDS or AIDS-related complex (ARC). Safety data for patients with AIDS or ARC are discussed in detail elsewhere (7).

Interspecies scaling of GLQ223 pharmacokinetic parameters are also presented. A linear correlation of pharmacokinetic data to species body weight, when plotted on a log-log scale, has been found for various drugs (2, 9, 11). Scaling of pharmacokinetic parameters is based on the concept that similarities in the anatomy, physiology, biochemistry, and cellular structure exist among numerous mammalian species and that various physiologic properties can be correlated well to species body weight (1, 10). Thus, since drug elimination is associated with physiological properties, it is reasonable that parameters that define the disposition of drugs can be scaled in mammals.

Allometric equations describing the relationship between pharmacokinetic parameters and body weight are used to predict the disposition of drugs in humans and, therefore, can be helpful in designing dosage regimens to be used in humans. Also, successful scaling can find an application in selecting dose and dosage intervals in studies of animal models. We attempted pharmacokinetic scaling for GLQ223 *a posteriori*; i.e., we used data obtained in rats, monkeys, and patients to determine allometric equations that may be useful for the prediction of doses and dosage regimens to be used in animal models of retroviral infection (5).

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MATERIALS AND METHODS

Animal studies. (i) Rats. Nine male Sprague-Dawley rats, housed in Nalgene metabolic cages with food and water available ad libitum, were studied. Five rats (weight, 330 ± 20 g) received 3,500 μg of GLQ223 per kg of body weight as a short intravenous infusion (2 min) via the caudal vein, one rat received vehicle alone (sterile saline solution), without GLQ223, and three rats (weight, 340 ± 30 g) received 3,500 μg of GLQ223 per kg as a single injection into the muscular mass of the hind leg.

From each animal, 1 ml of blood was collected by retro-orbital sinus puncture after light ether anesthesia at the following times after GLQ223 administration: 10, 20, 30, 60,

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120, 240, and 360 min. Blood samples were collected into chilled tubes containing EDTA as an anticoagulant. Plasma was harvested and frozen at −70°C until it was assayed.

Urine samples were collected from three of the rats that received the intravenous dose 24 h prior to and 6 h after dosing and were frozen at −70°C until they were assayed. All animals were observed once per hour for the first 4 h and then daily for 4 days after dosing for any clinical evidence of toxicity.

(ii) Monkeys. Four cynomolgus monkeys, housed in stainless steel cages of conventional design with food and water allowed ad libitum, were studied. Three monkeys, two females and one male (weight, 3.93 ± 0.85 kg), were given 300 μg of GLQ223 per kg of body weight as a short intravenous infusion (2 min) via the saphenous vein; one male received vehicle alone (sterile saline solution), without GLQ223. From each animal, 1 ml of blood was collected at the following times after GLQ223 administration: 5, 10, 15, and 30 min and 1, 2, 4, 6, 8, 12, and 24 h. Blood samples were collected into chilled tubes containing EDTA as an anticoagulant. Plasma was harvested and frozen at −70°C until it was assayed. All animals were observed hourly for the first 8 h and then daily for 4 days after dosing for any clinical evidence of toxicity.

Patient studies. Eighteen male patients, 10 with AIDS and 8 with ARC, were studied after giving informed consent. The study was approved by the Committee for Human Research, University of California, San Francisco.

Patient weights were within ±10% of their ideal body weights. The mean patient age was 39.5 years (range, 27 to 59 years). The patients enrolled in this study had normal kidney function (creatinine clearance, ≥80 ml/min) and acceptable liver function (serum glutamic oxalacetic transaminase and serum glutamic pyruvic transaminase, less than or equal to 1.5 times the upper limit of normal). Further details of this patient population are described in a previous report (7).

Drug administration to patients. Each patient received a single intravenous dose of GLQ223 as a short-term infusion (2 to 4 min). The doses administered were 1, 8, 16, 24, and 36 μg/kg of body weight. Six patients received the 24-μg/kg dose; at all other doses, three patients were studied.

Patients were hospitalized in the General Clinical Research Center and were kept under observation for a minimum of 48 h following dosing. Blood samples (2 ml) for GLQ223 analysis were obtained from the arm contralateral to that used for the drug infusion at the following times: 0, 5, 10, 20, 30, 45, 60, and 90 min and 2, 3, 4, 5, 6, 8, 10, 12, 16, 20, and 24 h postinfusion. EDTA-anticoagulated plasma samples were immediately placed on ice and centrifuged, and the plasma was removed and frozen at −70°C until it was assayed.

Analytical methods. Plasma GLQ223 concentrations in rats, monkeys, and humans were quantitated at Genelabs by a sensitive capture sandwich enzyme-linked immunosorbent assay.

Briefly, a solid-phase-coupled GLQ223-reactive murine monoclonal antibody was used to capture the antigen from test samples, a protein A-purified immunoglobulin G fraction from a polyclonal GLQ223-reactive rabbit serum was used for the detection of bound antigen, and an alkaline phosphatase-labeled goat anti-rabbit immunoglobulin G conjugate was used with *p*-nitrophenyl phosphate substrate for signaling.

The optical density values plotted against log GLQ223 concentrations were linear in the range of 0.5 to 16.0 μg of GLQ223 per liter. The lower limit of quantitation was 0.5 μg/liter.

Intraday and interday variability, respectively, were 6.3 and 16.8% (n = 12) at a plasma GLQ223 concentration of 2 μg/liter, 8.9 and 10.4% (n = 12) at a concentration of 20 μg/liter, and 4.3 and 11.8% (n = 12) at a concentration of 200 μg/liter. Two dilutions were tested for each of the concentrations in plasma of 2 μg/liter (1:1 and 1:2), 20 μg/liter (1:8 and 1:16), and 200 μg/liter (1:160 and 1:320). Since no difference associated with dilution was observed, the calculated concentrations were averaged to evaluate interday and intraday variabilities.

The assay was not appreciably affected by the presence of plasma or EDTA. Every plasma sample was measured at least in duplicate, and the mean value was used for pharmacokinetic analysis.

Pharmacokinetic analysis. Pharmacokinetic parameter estimates were obtained by a computer program by using an iterative, nonlinear, weighted least-squares regression analysis with the Powell minimization algorithm (SIPHAR release 3.3 by SIMED). Choices between models were made by comparing Akaike, Schwartz, and Leonard values generated from this program.

The weighting factor was chosen by visual inspection of the fitted line. The weighting factors analyzed were 1, $1/y$, and $1/y^2$, where y is the calculated concentration.

Model-dependent parameters were computed by using the following equations: $AUC_{0-\infty} = \Sigma\ Coef_i/Exp_i$, where $AUC_{0-\infty}$ is the area under the plasma concentration-time curve from time zero to infinity, and $Coef_i$ and Exp_i are the coefficients and exponents defining the ith compartment, respectively; CL (plasma clearance) = dose/$AUC_{0-\infty}$; MRT (mean residence time) = $(\Sigma\ Coef_i/Exp_i^2)/AUC_{0-\infty}$; V_{ss} (volume of distribution at steady state) = CL × MRT; and V_β (volume of distribution during the elimination phase) = CL/k_{el}, where k_{el} is the terminal elimination rate constant. Half-lives ($t_{1/2}$) for each compartment were calculated by dividing the respective rate constants into ln 2. Percent coefficients of variation for computed coefficients and exponents were calculated as (SD/P) × 100, where SD is the standard deviation computed by using the variance-covariance matrix, and P is the relative coefficient or exponent.

Noncompartmental analysis was also carried out by standard methods (6) for confirmation of modeling results.

Statistical analysis. To test the relationship between dose and various pharmacokinetic parameters, two different methods were used. (i) The slope of the regression analysis line correlating the dose and pharmacokinetic parameter was tested against the hypothesis that the median slope was equal to zero, and (ii) superposition of the dose/body weight normalized plasma concentration-time curves was used.

Interspecies scaling. Allometric scaling of CL (in liters per hour), V_{ss} (in liters), and elimination $t_{1/2}$ ($t_{1/2\beta}$) was accomplished by using the heterogonic equation $Y = aW^b$, where Y is the pharmacokinetic parameter, W is the weight, a is the value of Y for a hypothetical 1-kg animal, and b is the proportionality coefficient between Y and W. The values a and b were calculated by using the log-log plot of Y versus W, where a is the y intercept and b is the slope of the logarithmic transformation of the allometric equation: $\log Y = \log a + b \log W$. To determine whether the slope (b) of the linear regression log Y versus log W was significantly different from 0, t test statistics were applied, assuming that all parameters from each animal are known with the same precision and that there are no dose dependencies within the tested dose range.

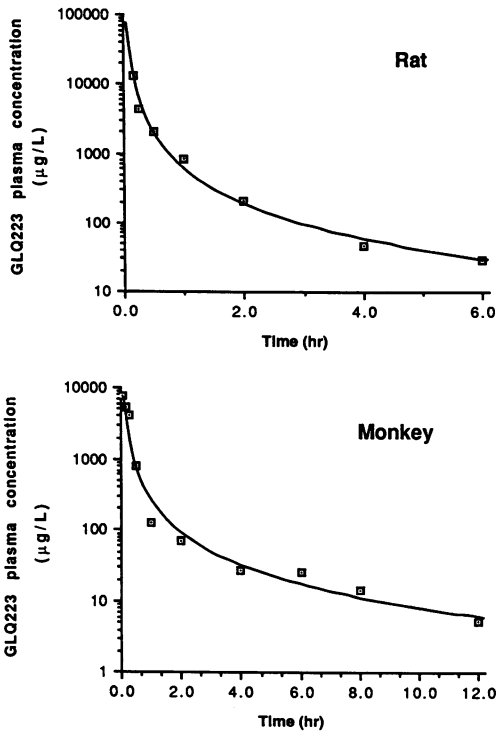

FIG. 1. Plasma concentration-time profile of GLQ223 in rats and monkeys.

A plot described by Dedrick et al. (4) (Dedrick plot) was used to evaluate whether the mean concentration-time profiles were superposable after normalization of the y axis (concentration) by dividing concentrations in plasma by the dose per unit body weight and after normalization of the x axis (time) by dividing the time after injection by $W^{0.25}$, where the choice of $W^{0.25}$ as the correction factor for time is based on the concept that "equivalent time" between species correlates with weight to the 0.25 power (12).

A Dedrick plot with transformation of the x axis as proposed by Boxenbaum and Ronfeld (3) was also considered. Biologic time for each species was assumed to be equal to $t/W^{b'-b}$, where b' and b are the allometric exponents relating V_{ss} and CL to body weight, respectively. In this way, equivalent time is computed by using intrinsic factors of the drug instead of an empirical value, as in the elementary Dedrick plot. For this plot, concentrations are normalized to dose per body weight at b' power.

RESULTS

A representative concentration-time profile for rats and monkeys is shown in Fig. 1. The best description of the decay of plasma concentration versus time was made by using a two-exponent model. All rat and monkey data sets were best fit by using a weighting factor equal to $1/y^2$.

The mean values of pharmacokinetic parameters of GLQ223 in rats and monkeys are given in Table 1. The mean CL was 0.85 ± 0.24 liter/h/kg in rats and 0.16 ± 0.08 liter/h/kg in monkeys. The V_{ss} averaged 0.42 ± 0.12 liter/kg in rats and 0.21 ± 0.20 liter/kg in monkeys. The $t_{1/2\beta}$s were 1.3 ± 0.4 and 3.7 ± 1.5 h in rats and monkeys, respectively. GLQ223 was not detectable in urine samples from any animals.

TABLE 1. Mean pharmacokinetic parameters of GLQ223 in rats and monkeys[a]

Animal, dose (μg/kg)	No. of animals	AUC (μg · h/liter)	CL (liter/h)	CL (liter/h/kg)	$t_{1/2\alpha}$ (h)	$t_{1/2\beta}$ (h)	V_{ss} (liter)	V_{ss} (liter/kg)	V_β (liter)	V_β (liter/kg)	MRT (h)
Rat, 3,500	5	4,367.9 ± 1,189.0	0.28 ± 0.06	0.85 ± 0.24	0.13 ± 0.04	1.3 ± 0.4	0.14 ± 0.03	0.42 ± 0.12	0.52 ± 0.17	1.58 ± 0.56	0.5 ± 0.1
Monkey, 300	3	2,165.6 ± 853.9	0.46 ± 0.10	0.16 ± 0.08	0.15 ± 0.04	3.7 ± 1.5	0.55 ± 0.40	0.21 ± 0.20	2.56 ± 1.63	0.95 ± 0.85	1.1 ± 0.5

[a] Values are means ± standard deviations. $t_{1/2\alpha}$, distribution half-life; all other abbreviations are defined in the text.

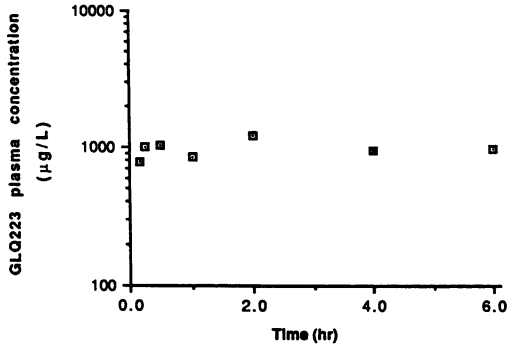

FIG. 2. Concentrations in plasma after intramuscular administration of 3,500 μg of GLQ223 per kg of body weight to rats.

When GLQ223 was given to rats intramuscularly as a single dose of 3,500 μg/kg, concentrations in plasma measured approximately 1,000 μg/liter over the entire 6-h period of sampling (Fig. 2). No signs of toxicity were recognized in rats or monkeys at the administered doses.

The mean plasma GLQ223 concentrations after a slow intravenous injection of each of the five dosage regimens into patients with AIDS and ARC patients are shown in Fig. 3.

Plasma GLQ223 concentration-time profiles were best fit to a two-compartment open model for patients 4 to 18 by using $1/y^2$ as the weighting factor (except for subject 4, for whom $1/y$ was used). For patients 1, 2, and 3, who received the lowest dose (1 μg/kg), the data were best described by a one-compartment model with weight $1/y$, since plasma GLQ223 levels were not measurable after 1 to 1.5 h. For this reason, data obtained from patients on this dosage regimen were not considered to represent accurately the total GLQ223 disposition. Coefficients of variation for estimates of coefficients and exponents were never greater than 11% for all curve fits.

Table 2 provides the values of the mean pharmacokinetic parameters for each group of patients over the dosage range of 1 to 36 μg/kg. CL ranged from 0.16 liter/h/kg for the

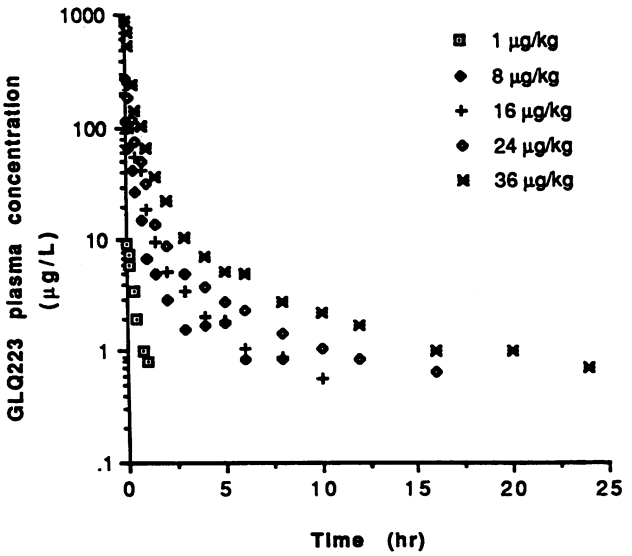

FIG. 3. Mean plasma GLQ223 concentration-time profiles for patients with AIDS or ARC.

TABLE 2. Mean pharmacokinetic parameters of GLQ223 in patients with AIDS or ARC[a]

Dose (μg/kg)	No. of subjects	C_{max} (μg/liter)	AUC (μg · h/liter)	CL (liter/h)	CL (liter/h/kg)	$t_{1/2\alpha}$ (h)	$t_{1/2\beta}$ (h)	V_{ss} (liter)	V_{ss} (liter/kg)	V_β (liter)	V_β (liter/kg)	MRT (h)
1	3	9 ± 2	5 ± 2	13.4 ± 3.6	0.20 ± 0.08	0.31 ± 0.06[b]		5.9 ± 0.6[b]	0.09 ± 0.02[b]			0.4 ± 0.1
8	3	113 ± 66	80 ± 54	11.0 ± 9.1	0.16 ± 0.14	0.27 ± 0.04	2.4 ± 0.7	10.8 ± 5.3	0.16 ± 0.09	33.7 ± 19.1	0.49 ± 0.31	1.2 ± 0.3
16	3	196 ± 33	159 ± 23	7.2 ± 0.8	0.10 ± 0.02	0.38 ± 0.02	3.1 ± 0.1	10.0 ± 2.1	0.14 ± 0.02	32.3 ± 3.2	0.46 ± 0.08	1.4 ± 0.1
24	6	254 ± 28	157 ± 30	10.7 ± 2.3	0.16 ± 0.03	0.29 ± 0.06	3.1 ± 1.0	15.8 ± 5.4	0.23 ± 0.07	46.5 ± 15.5	0.68 ± 0.20	1.5 ± 0.5
36	3	876 ± 60	396 ± 29	6.7 ± 0.6	0.09 ± 0.00	0.30 ± 0.10	4.3 ± 1.2	11.5 ± 4.4	0.15 ± 0.04	41.3 ± 14.3	0.55 ± 0.12	1.7 ± 0.5
Patient mean ± SD[c]				9.2 ± 4.2	0.13 ± 0.07	0.31 ± 0.06	3.2 ± 1.0	12.8 ± 5.0	0.18 ± 0.07	40.1 ± 14.4	0.57 ± 0.20	1.5 ± 0.4

[a] Values are means ± standard deviations. C_{max}, maximum concentration of drug in serum; $t_{1/2\alpha}$, distribution half-life; all other abbreviations are defined in the text.
[b] At this dose, $t_{1/2}$ and volume of distribution are with respect to a one-compartment model.
[c] Values are means ± standard deviations for all patients when the data obtained from the patient who received the 1-μg/kg dose are omitted.

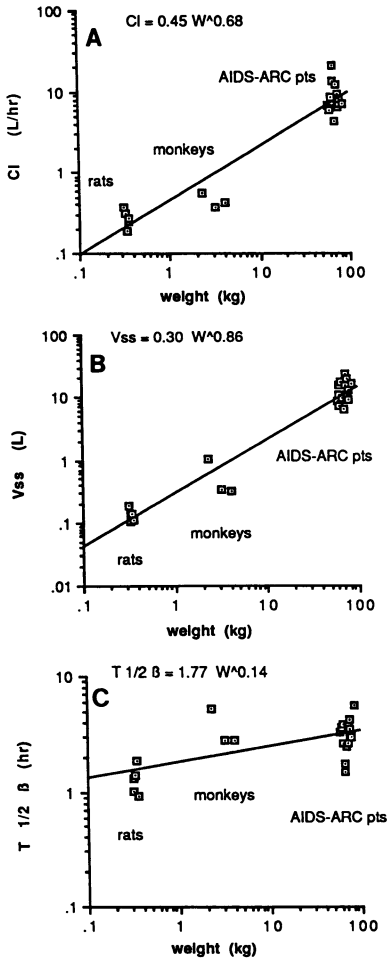

FIG. 4. Allometric relationship between CL (A), V_{ss} (B), and $t_{1/2\beta}$ (C) as a function of body weight.

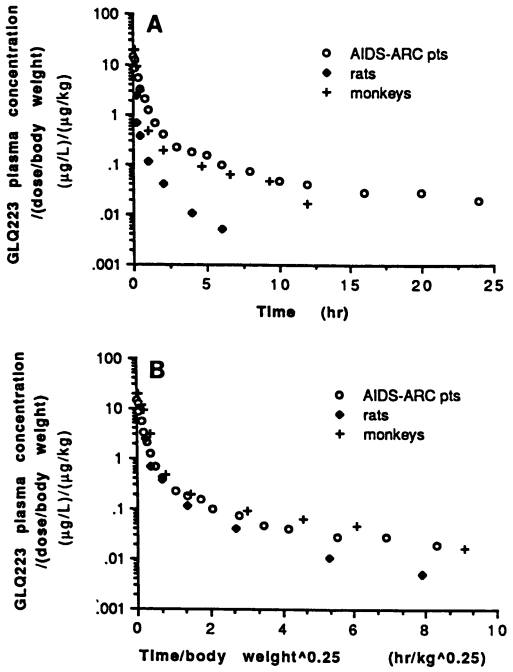

FIG. 5. Plasma GLQ223 concentrations normalized for dose per species body weight plotted versus chronologic time (A) and biologic time (Dedrick plot) (B).

8-µg/kg dose to 0.09 liter/h/kg for the 36-µg/kg dose. V_{ss} exhibited a range of 0.16 to 0.15 liter/kg at the 8- and 36-µg/kg doses. Following the initial decline in plasma, GLQ223 was eliminated with $t_{1/2\beta}$ ranging from 2.4 to 4.3 h over the 8- to 36-µg/kg dose range.

The slope of the linear regression curve of V_{ss} and CL, both corrected and not corrected per body weight, versus administered dose was not statistically different from the null hypothesis of a slope of zero. This indicates no dependency on the dose for these two parameters. Apparent dose dependency was observed for $t_{1/2\beta}$ and V_β, both of which showed a tendency to increase with increasing dose ($r^2 = 0.314$ [$P < 0.01$] and $r^2 = 0.075$ [$P < 0.01$], respectively).

Allometric scaling results are shown in Fig. 4. CL showed a good linear correlation to body weight ($r^2 = 0.915$; $P < 0.001$), as did V_{ss} ($r^2 = 0.948$; $P < 0.001$), while $t_{1/2\beta}$ correlated poorly with weight ($r^2 = 0.409$; $P < 0.01$).

A plot of concentrations in plasma normalized for dose per species body weight versus time for rats, monkeys, and patients with AIDS or ARC (Fig. 5A) shows that GLQ223 elimination from plasma was faster in smaller animals.

When concentrations in plasma were plotted versus time profiles with axis corrections as proposed by Dedrick et al. (4) (Fig. 5B), a good superposition was found for patients with AIDS or ARC and monkey datum points, while concentrations in plasma per dose per body weight in rats were slightly lower, especially in the terminal phase of GLQ223 disposition. Axis transformation as indicated by Boxenbaum and Ronfeld (3) did not result in better superposition of the curves compared with that of the elementary Dedrick plot (data not shown).

DISCUSSION

This is the first study in patients with AIDS and ARC describing the disposition of GLQ223, a relatively new compound with in vitro anti-HIV activity.

GLQ223 exhibited a short distribution phase followed by a slower elimination phase with a $t_{1/2\beta}$ of approximately 3.5 h. No information is available regarding the elimination mechanisms for this drug. Renal clearance does not seem to be important since GLQ223 is not found unchanged in the urine. The liver, the reticuloendothelial system, or other pathways may be involved in GLQ223 elimination, most likely through mechanisms involving proteolytic degradation of the compound.

The V_{ss} for GLQ223 was only approximately 11 liters. This is less than the volume of extracellular fluid for a 70-kg male human (16 liters). Whether the V_{ss} of GLQ223 simply represents an actual portion of the extracellular fluid or whether the drug is taken up extensively by blood cells or tissue cells is unknown.

The values for CL and V_{ss} for GLQ223 did not significantly change with the different doses administered.

Superposition of the plasma concentration-time profiles following each dose after normalization of the concentration values to the respective dose per body weight does not suggest a dose dependency for GLQ223 disposition (Fig. 6). Apparent dose dependency was seen for $t_{1/2\beta}$, V_β, and MRT. The increase in $t_{1/2\beta}$ with increasing dose is probably an

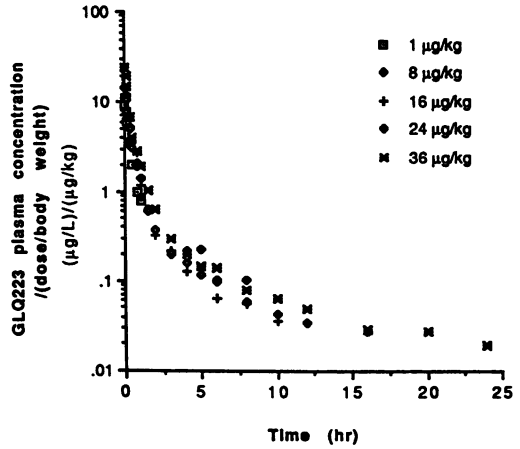

FIG. 6. Plasma GLQ223 concentration-time profiles for patients with AIDS or ARC with concentrations normalized for dose per patient body weight.

artifact caused by the greater number of datum points available for nonlinear regression of the terminal phase of the concentration-time curve at higher doses. Accordingly, the estimates of V_β and MRT are also affected since these parameters are dependent on the k_{el}.

No evidence of efficacy in terms of HIV antigen reduction or clinical improvement was observed for patients with AIDS and ARC in this study. Because this was a single-dose phase I study, this finding is not unexpected. GLQ223 activity against HIV has been shown in in vitro studies in which macrophage/monocyte cells obtained from patients with HIV infection were exposed to 500 μg/liter for a single 3-h time period. In addition, GLQ223 was able to inhibit HIV p24 antigen expression in in vitro-infected cells of the lymphocyte lineage at concentrations of 16 μg/liter after 4 days of incubation, the time of maximum virus production in this assay system.

In our study the mean peak concentration in plasma after the 24-μg/kg dose was 271 μg/liter; this declined to 8.8 μg/liter at 2 h after administration. Following the 36-μg/kg dose, average peak concentrations were 876 μg/liter; after 2 h the concentration was 22.8 μg/liter, and it was approximately 1 μg/liter at 20 h after the dose. Thus, it is possible that the lack of efficacy in this study was caused by an insufficient exposure time to adequate levels of GLQ223. Subsequent clinical testing of the compound has involved administration via two infusions in which a loading dose has been combined with a sustained infusion over 2 to 3 h, in an effort to achieve and maintain concentrations of the drug in plasma that have been shown to have in vitro antiviral action (6a).

Although the mechanism of action that underlies the anti-HIV activity of trichosantin is not known, GLQ223 belongs to the family of single-chain ribosome-inactivating proteins which inhibit in vitro translation in cell-free systems (15), and therefore, its activity is likely to be related to ribosomal function inhibition. In addition, in vitro studies showed that GLQ223 induces a selective proportional decrease in the amount of viral RNA relative to the amount of total cellular RNA, suggesting a possible selective effect of GLQ223 on viral nucleic acid synthesis, processing, or stability (8).

Data for scaling of pharmacokinetic parameters were available from only two animal species and from patients with AIDS and ARC. Nevertheless, a linear correlation with a high r^2 value was found for CL and V_{ss} versus weight on a log-log scale, indicating the similarity and linearity in the overall disposition of GLQ223 in different mammalian species.

In general, smaller animals eliminate drugs more rapidly than do larger animals, as can be seen for GLQ223 in Fig. 5A, in which concentrations in plasma normalized to dose per body weight are plotted against time. However, it has been shown that when the biologic time is substituted for the chronologic time (Dedrick plot), disposition profiles are superposable for drugs that are characterized by first-order kinetics, that are not highly lipid soluble, and that are not strongly or nonlinearly bound to proteins in plasma or tissue.

A Dedrick plot for GLQ223 shows that the disposition profiles for the monkeys and patients with AIDS and ARC are superposable, while rats had slightly lower concentrations in plasma in the terminal phase of the curve. This indicates that rats eliminate the drug relatively faster, even when their own biologic time is used in an attempt to normalize the x axis to the equivalent time among species. This observation, reflecting the poor correlation of $t_{1/2\beta}$ with weight, may be truly based on physiological aspects of GLQ223 elimination or it may be an artifact caused by the fewer number of datum points available for the calculation of $t_{1/2\beta}$ in rats.

A further interesting observation that emerged from the animal studies was the slow release of GLQ223 by muscle into plasma after intramuscular administration to rats, which caused constant concentrations in plasma over a 6-h period. This could be relevant to future GLQ223 development, since intramuscular administration may be an alternative route of administering the drug. However, the AUC up to 6 h after intramuscular administration was greater than that after an intravenous injection of the same 3,500-μg/kg dose. This observation is not easily explainable and deserves further investigation.

In conclusion, we characterized the pharmacokinetics of GLQ223 in rats, monkeys, and patients with AIDS and ARC. Interspecies scaling of pharmacokinetic parameters suggest that the drug is characterized by a similarity in disposition in different mammalian species. Allometric equations relating pharmacokinetic parameters to body weight may be useful in forecasting the doses and dosage regimens to be used in animal models. Pharmacokinetic data obtained from patients with AIDS and ARC will be useful in designing future studies for the evaluation of the toxicity and efficacy of GLQ223 in HIV-infected patients.

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REFERENCES

1. **Adolph, E. F.** 1949. Quantitative relation in the physiological constitutions of mammals. Science **109**:579–585.
2. **Boxenbaum, H.** 1982. Interspecies scaling, allometry, physiological time, and ground plan of pharmacokinetics. J. Pharmacokinet. Biopharm. **10**:201–227.
3. **Boxenbaum, H., and R. Ronfeld.** 1983. Interspecies pharmacokinetic scaling and the Dedrick plots. Am. J. Physiol. **245**:R768–R774.
4. **Dedrick, R. L., K. B. Bischoff, and D. S. Zaharko.** 1970. Interspecies correlation of plasma concentration history of methotrexate (NSC-740). Cancer Chemother. Rep. **54**:95–101.
5. **Esparza, J.** 1990. Animal models for the evaluation of drugs and vaccines for HIV infection and AIDS: report of a WHO working group. Dev. Biol. Stand. **72**:367–372.

6. **Gibaldi, M., and D. Perrier.** 1982. Pharmacokinetics, 2nd ed. Marcel Dekker, Inc., New York.
6a. **Kahn, J. O., et al.** Unpublished data.
7. **Kahn, J. O., D. K. Lawrence, J. G. Gambertoglio, C. J. Arri, L. Turin, T. Kibort, R. L. Williams, J. D. Lifson, and P. A. Volberding.** 1990. The safety and pharmacokinetics of GLQ223 in subjects with AIDS and AIDS-related complex: a phase I study. AIDS **4**:1197–1204.
8. **McGrath, M. S., K. M. Hwang, S. E. Caldwell, I. Gaston, K.-C. Luk, et al.** 1989. GLQ223: an inhibitor of human immunodeficiency virus replication in acutely and chronically infected cells of lymphocyte and mononuclear phagocyte lineage. Proc. Natl. Acad. Sci. USA **86**:2844–2848.
9. **Mordenti, J.** 1985. Forecasting cephalosporin and monobactam antibiotic half-lives in humans from data collected in laboratory animals. Antimicrob. Agents Chemother. **27**:887–981.
10. **Mordenti, J.** 1986. Man versus beast: pharmacokinetic scaling in mammals. J. Pharm. Sci. **75**:1028–1040.
11. **Patel, B. A., F. D. Boudinot, R. F. Schinazi, J. M. Gallo, and C. K. Chu.** 1990. Comparative pharmacokinetics and interspecies scaling of 3′-azido-3′-deoxy-thimidine (AZT) in several mammal species. J. Pharmacobio-Dyn. **13**:206–211.
12. **Sthal, W. R.** 1962. Similarity and dimensional method in biology. Science **137**:205–212.
13. **Wang, Y., R. Q. Qian, Z. W. Gil, S. W. Jin, L. Q. Zhang, Z. X. Xia, G. Y. Tian, and C. Z. Ni.** 1986. Scientific evaluation of Tian Hua Fen (THF)—history, chemistry and application. Pure Appl. Chem. **58**:789–798.
14. **Yeung, H. W., D. M. Wong, T. B. Ng, and W. W. Li.** 1986. Purification of three isolectins from root tubers of *Trichosantes kirilowii* (Tianhuafen). Int. J. Pept. Protein Res. **27**:325–333.
15. **Zhang, X., and J. Wang.** 1982. Homology of trichosantin and ricin A chain. Nature (London) **321**:477–478.