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Pharmacokinetics of 2′,3′-Dideoxycytidine in Rats: Application to Interspecies Scale-up

SAFAA S. IBRAHIM AND F. DOUGLAS BOUDINOT

Department of Pharmaceutics, College of Pharmacy, University of Georgia, Athens, GA 30602, USA

Abstract—The effects of dose on the pharmacokinetics of 2′,3′-dideoxycytidine (DDC), a potent inhibitor of HIV replication, have been studied in rats. DDC was administered intravenously at doses of 10, 50, 100 and 200 mg kg^{-1}. Plasma and urine drug concentrations were determined by HPLC. Non-compartmental pharmacokinetic parameters were calculated by area/moment analysis. DDC plasma concentrations declined rapidly with a terminal half-life of $0{\cdot}98 \pm 0{\cdot}18$ h (mean ± s.d.). No statistically significant differences were observed in pharmacokinetic parameters between the four doses. Total, renal and non-renal clearance values were independent of dose and averaged $1{\cdot}67 \pm 0{\cdot}24$, $0{\cdot}78 \pm 0{\cdot}11$, and $0{\cdot}89 \pm 0{\cdot}27$ L h^{-1} kg^{-1}, respectively. Approximately 50% of the dose was excreted unchanged in urine. Steady state volume of distribution was also independent of dose and averaged $1{\cdot}2 \pm 0{\cdot}21$ L kg^{-1}. Protein binding of DDC to rat serum proteins was independent of drug concentration with the fraction of drug bound averaging $0{\cdot}45 \pm 0{\cdot}12$. Thus, the disposition pattern of DDC in the rat is independent of the administered dose even at high doses. Significant interspecies correlations were found for total, renal and non-renal clearance and steady state volume of distribution. Interspecies scaling resulted in superimposable plasma DDC concentration-time profiles from four laboratory animal species and man. Thus, plasma DDC concentrations in humans can be predicted from pharmacokinetic parameters obtained in laboratory animals.

2′,3′-Dideoxycytidine (DDC), a pyrimidine nucleoside, powerfully and selectively inhibits the replication of human immunodeficiency virus (HIV) (Cooney et al 1986; Dahlberg et al 1987; Mitsuya et al 1987; Waqar et al 1984), the causative agent of acquired immunodeficiency syndrome (AIDS) and related diseases (Barre-Sinoussi et al 1983; Gallo et al 1984). This anti-HIV action results from the intercellular conversion of DDC to the 5′-triphosphate metabolite which interacts with retroviral reverse transcriptase and inhibits virus replication. On a molar basis, DDC is ten times more potent than zidovudine (AZT) with complete in-vitro inhibition of HIV obtained at a concentration of 0·11 μg mL^{-1} (0·5 μM) (Mitsuya & Broder 1986). It is relatively resistant to cytidine deaminase, a major catabolic enzyme for cytidine analogues (Cooney et al 1986).

Phase I clinical trials of 2′,3′-dideoxycytidine in patients with AIDS are currently being conducted (Klecker et al 1988; Yarchoan et al 1988). The drug has the capacity to inhibit the in-vivo replication of HIV as measured by P24 antigenaemia. Dose-related toxic effects included cutaneous eruptions, fever, mouth sores, thrombocytopaenia and neutropaenia. In some patients reversible painful peripheral neuropathy has developed. Peak plasma DDC concentrations were approximately proportional to the dose administered with a peak concentration of 0·11 μg mL^{-1} (0·5 μM) being attained with a 1 h infusion of 0·06 mg kg^{-1}.

The disposition of DDC has recently been examined in several laboratory animal models including the mouse, monkey (Kelley et al 1987) and cat (Kalin & Hill 1988). The application of pharmacokinetic data obtained in animal models to the clinical setting has been enhanced by interspecies scaling techniques (Dedrick et al 1970; Boxenbaum 1982). Employing allometric relationships, reliable predictions of drug concentrations and distribution in man can be derived from pharmacokinetic data yielded in laboratory animal studies. Information gained from animal models can thus enable more efficient drug screening, provide a basis for clinical trials and enhance the design of optimal therapeutic regimens.

The rat is a well suited animal model for pharmacokinetic studies. These animals are easily handled, relatively large sample volumes can be obtained and serial blood samples can be taken. Pharmacokinetic data in the rat has also been shown to be useful for predicting disposition characteristics of drugs in man employing interspecies scale-up methods (Boxenbaum 1982; Igari et al 1983). The purpose of the present study was to characterize the pharmacokinetics of 2′,3′-dideoxycytidine in the rat and to assess the effects of dose on drug disposition following intravenous administration. In addition, results of this study were combined with previously reported pharmacokinetic data after DDC administration to mice, cats, monkeys and human patients to provide a basis for interspecies scale-up of the disposition characteristics of the drug.

Correspondence to: F. D. Boudinot, Department of Pharmaceutics, College of Pharmacy, University of Georgia, Athens, GA 30602, USA.

Materials and Methods

Chemicals

2′,3′-Dideoxycytidine (DDC) was provided by Dr Karl Flora, National Cancer Institute (Bethesda, MD) with purity exceeding 98%. 5-Bromo-2′-deoxyuridine (BDU) was purchased from Sigma Chemical Co. (St. Louis, MO). Methanol, HPLC grade, was obtained from J. J. Baker (Phillipsburg, NJ). All other reagents and chemicals were of analytical grade and were obtained from J. J. Baker.

Pharmacokinetic studies

Adult male Sprague-Dawley rats, 250–350 g, were used. External jugular vein cannulas were inserted under light ether anaesthesia the day before the experiment. Food was withdrawn the night before and during the study; however, water was freely available. Rats received 10, 50, 100 or 200 mg kg^{-1} DDC administered intravenously in 1·0 mL normal saline over 30 s via the jugular vein cannula. Blood samples (0·25 mL) were collected at 0·08, 0·25, 0·5, 0·75, 1, 1·5, 2, 3, 4, 5, 6, 7, 8, 10 and 12 h from the cannula into heparinized polypropylene micro-centrifuge tubes. Preliminary studies demonstrated no adsorption of DDC to cannulas. Blood volume was replaced with an equal volume of 0·9% NaCl (saline). Plasma (0·1 mL) was immediately harvested and frozen at −20°C until analysis. Urine was collected at 6 h intervals for 24 h. Urine volume was measured and an aliquot was frozen at −20°C until analysis.

Protein binding

The binding of DDC to rat serum proteins was determined by equilibrium dialysis. Pooled rat serum (0·4 mL), spiked with DDC to yield concentrations in the range 1–500 μg mL^{-1}, was dialysed against an equal volume of isotonic sodium phosphate buffer, pH 7·4, using Plexiglass cells and Spectrapor II membrane (Spectrum Medical Industries, New York, NY) with a molecular weight cut-off of 12 000–14 000. Three replicates of each concentration were performed. After equilibrating for 16 h (determined from preliminary experiments) at 37°C with gentle agitation, serum and buffer were analysed for DDC. Appropriate correction for fluid shifts that occurred during dialysis were made and percent of drug bound was calculated (Boudinot & Jusko 1984).

Analytical methodology

Reversed phase high performance liquid chromatography (HPLC) (Kelley et al 1987) with minor modifications was used for the determination of DDC in plasma. Plasma (100 μL), BDU (20 μg mL^{-1}) as an internal standard (50 μL), and trichloroacetic acid (10%) as a protein precipitant (50 μL) were added to polypropylene micro-centrifuge tubes, vortexed for 30 s and centrifuged at 7000 rev min^{-1} for 5 min. Supernatant (20–100 μL) was injected onto the HPLC (Waters Associates, Milford, MA). The separation was performed on an Alltech Econosphere ODS Column (0·46 × 25 cm, 5 μm particle size, Alltech Associates, Deerfield, IL) with a mobile phase consisting of 10% methanol in phosphate buffer, pH 6·8, at a flow rate of 1·0 mL min^{-1}. Detection was at 254 nm.

Urine samples were diluted 1:100 with HPLC, mobile phase, internal standard was added and 20–100 μL of sample was injected onto the HPLC. Drug concentration was multiplied by volume of urine collected to determine the amount of unchanged DDC excreted within 24 h postdose.

Peak height ratios were used to construct standard curves for DDC. Standard curve slopes and intercepts were generated by weighted (1/y) least squares linear regression. The assay was linear in the range of 0·1–100 μg mL^{-1} with a lower limit of quantitation of 0·1 μg mL^{-1}. Extraction recovery of the drug and internal standard was 90%. Intra- and inter-day coefficients of variation for the assay were less than 4 and 7%, respectively.

Pharmacokinetic analysis

Area/moment analysis was used to calculate pharmacokinetic parameters of DDC. Area under the plasma concentration-time curve (AUC) and first non-normalized moment (AUMC) were determined by Lagrange polynomial interpolation and integration (Rocci & Jusko 1983) from time zero to the last sample time with extrapolation to time infinity using the least-squares terminal slope. Total clearance (CL_T) was calculated from Dose/AUC, mean residence time (MRT) from AUMC/AUC and steady state volume of distribution (V_{ss}) from $CL_T \times MRT$.

The fraction of drug excreted unchanged in urine (fe) was calculated from Au^{∞}/Dose, where Au^{∞} is the amount of DDC excreted to time infinity. No drug was detected in urine from the last sample collection interval, therefore, the measured amount of drug recovered in urine reflected Au^{∞}. Renal clearance (CL_R) was calculated from fe · CL_T, and non-renal clearance (CL_{NR}) from CL_T–CL_R.

One way analysis of variance (ANOVA) was used for evaluating the statistical significance between pharmacokinetic parameters for the four treatments. A probability level of less than 0·05 was considered statistically significant.

Interspecies scale-up

Plasma DDC concentration versus time data after intravenous administration to mice, monkeys (Kelley et al 1987), cats (Kalin & Hill 1988) and patients (Klecker et al 1988) were taken from the literature. Pharmacokinetic parameters were also extracted from these reports or, if not provided, were calculated from the plasma DDC concentration-time profiles using non-compartmental analysis. Correlations between pharmacokinetic parameters and species body weight were generated using allometric relationships (Boxenbaum 1982). Total clearance, renal clearance, non-renal clearance, and steady state volume of distribution values for mice, rats, cats, monkeys and man were plotted against species body weight according to the allometric relationship:

$$PK = aW^b$$

or

$$\text{Log } PK = \log a + b \cdot \text{Log } W$$

where PK is the pharmacokinetic parameter, W is the animal body weight and a and b are intercept and slope values generated by linear least squares regression analysis of logarithmically transformed data. Statistical significance of correlations were examined using the Student's *t*-test. 2′,3′-Dideoxycytidine concentration-time curves were scaled-up by plotting DDC concentration normalized by dose per body weight versus time normalized by body weight raised to the power 1-b, where b is the slope of the allometric plot of Log CL_T versus Log W.

Results and Discussion

A purpose of this experiment was to characterize the disposition of DDC in rats and to examine the effects of dose on the pharmacokinetics of the drug. The doses of DDC administered to rats were relatively large in comparison to those given to patients in clinical trials. Plasma DDC concentrations decline very rapidly in the rat (Fig. 1); thus, to

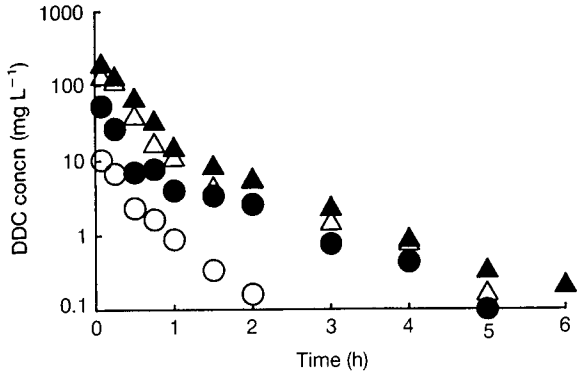

FIG. 1. Plasma concentrations of DDC in rats after intravenous administration of 10 (○), 50 (●), 100 (△) and 200 (▲) mg kg^{-1}.

adequately characterize the disposition of DDC, larger doses must be administered. Indeed, plasma DDC concentrations were measurable for only 2 to 3 h following 10 mg kg^{-1}, whereas DDC levels were detectable up to 6 h after higher doses. In clinical trials (Klecker et al 1988), DDC concentrations fell below the limit of assay quantitation 2 to 3 h after termination of intravenous infusion (1 h) of 0·03 to 0·09 mg kg^{-1} DDC. The doses of DDC administered to rats in this study are similar to those given to mice (100 mg kg^{-1}) and monkeys (27 mg kg^{-1}) for pharmacokinetic investigations (Kelley et al 1987). In addition, assessment of DDC pharmacokinetics over a wide range of doses will provide a basis for further pharmacodynamic and toxicologic studies. No obvious toxicity due to DDC administration was noted at any of the doses.

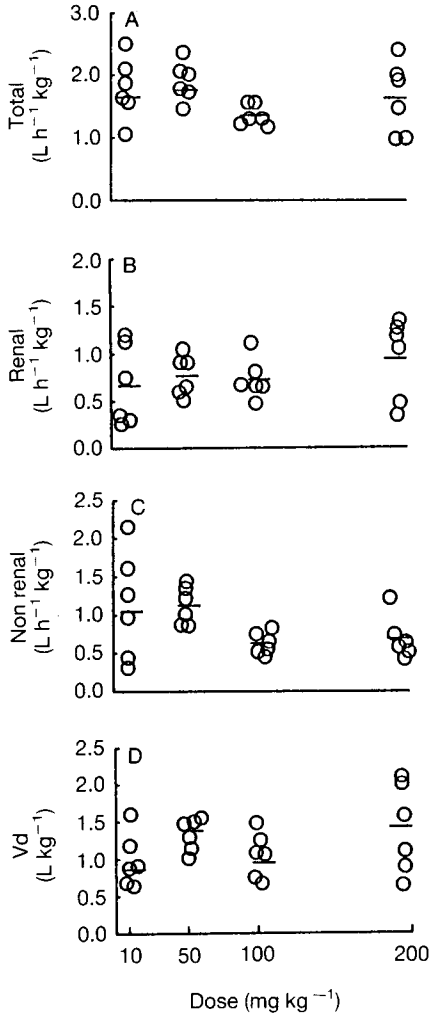

FIG. 2. Total clearance (A), renal clearance (B), nonrenal clearance (C) and steady state volume of distribution (D) of DDC as a function of dose in rats.

Table 1. Pharmacokinetic parameters following intravenous administration of 10, 50, 100 and 200 mg kg^{-1} DDC to rats.

	Dose, mg kg^{-1}			
Parameter[a]	10	50	100	200
Weight, kg	0·323 (0·02)	0·350 (0·03)	0·330 (0·02)	0·337 (0·02)
AUC, mg h L^{-1}	6·00 (1·88)	26·94 (4·46)	68·43 (14·40)	137·21 (52·90)
CL_T, L h^{-1} kg^{-1}	1·65 (0·39)	1·76 (0·30)	1·35 (0·17)	1·63 (0·58)
CL_R, L h^{-1} kg^{-1}	0·67 (0·43)	0·77 (0·21)	0·73 (0·22)	0·94 (0·43)
CL_{NR}, L h^{-1} kg^{-1}	1·05 (0·66)	1·13 (0·25)	0·62 (0·15)	0·69 (0·28)
Vss, L kg^{-1}	0·86 (0·22)	1·38 (0·22)	0·94 (0·39)	1·42 (0·65)
MRT, h	0·54 (0·13)	0·72 (0·21)	0·69 (0·11)	0·90 (0·39)
$t_{\frac{1}{2}}$, h	0·73 (0·45)	1·17 (0·55)	0·99 (0·20)	1·02 (0·31)

[a] Parameter values expressed as mean (s.d.) of six rats.

Representative plasma concentration-time profiles for DDC after intravenous administration of 10, 50, 100 and 200 mg kg^{-1} to rats are shown in Fig. 1. This figure illustrates the biexponential decline of DDC after each dose. The terminal half-life of DDC was independent of dose averaging 0·98 ± 0·18 h (mean ± s.d.). Total clearance (A), renal clearance (B), non-renal clearance (C) and steady state volume of distribution (D) as a function of dose are illustrated in Fig. 2. No statistically significant changes in any of these pharmacokinetic parameters with dose were found (Table 1). After the four doses, total clearance averaged 1·67 ± 0·24 L h^{-1} kg^{-1}, renal clearance 0·78 ± 0·11 L h^{-1} kg^{-1} and nonrenal clearance 0·89 ± 0·27 L h^{-1} kg^{-1}. Steady state volume of distribution averaged 1·2 ± 0·21 L kg^{-1} for the four doses. DDC also exhibited linear plasma protein binding with an average fraction bound value of 0·45 ± 0·12.

2′,3′-Dideoxycytidine is eliminated by the rat at a moderate rate as indicated by the CL_T value of 1·67 L h^{-1} kg^{-1}. Renal clearance (0·78 L h^{-1} kg^{-1}) accounted for approximately half of CL_T with 49 ± 8·1% of the dose recovered as unchanged DDC in urine. Urinary recovery of DDC was independent of the dose. Renal clearance is three-fold greater than glomerular filtration rate (creatinine clearance measured in four rats = 0·27 L h^{-1} kg^{-1}) indicating that DDC undergoes active tubular secretion.

Non-renal clearance accounted for approximately 50% of total clearance in the rat. The present study did not fully address evaluation of the mechanisms of non-renal elimination of DDC. However, urinary recovery studies failed to demonstrate the presence of a glucuronide metabolite sug-

gesting that glucuronidation is not a major elimination pathway for DDC in the rat. Kelley et al (1987) demonstrated that biliary excretion of unchanged DDC accounted for approximately 15% of total DDC clearance after intravenous drug administration in mice. While these investigators could not account for approximately 20% of the dose, they did show that metabolism by cytidine deaminase, a major catabolic enzyme for cytidine and cytidine analogues, and anabolism to the pharmacologically active mono-, di- and tri-phosphate anabolites, do not play a quantitatively important role in the disposition of DDC. No metabolic products were identified from clinical patient samples (Klecker et al 1988).

2′,3′-Dideoxycytidine appears to be widely distributed throughout the body since its steady state volume of distribution (1·2 L kg^{-1}) is greater than total body water (0·70 L kg^{-1}) of the rat (Gerlowski & Jain 1983). This is consistent with the findings of Kelley et al (1987) who showed that DDC significantly accumulated in kidney, liver, pancreas, lung, heart and thymus in mice. Thus, DDC exhibits straightforward, linear pharmacokinetics in the rat over a dose range of 10–200 mg kg^{-1}.

Animal models may provide insight into mechanisms of drug distribution and elimination that are not attainable from clinical studies and the results generated may be applicable to clinical circumstances. Pharmacokinetic profiles for DDC have been reported for several animal models including the mouse, monkey (Kelley et al 1987), and cat (Kalin & Hill 1988) as well as for patients with AIDS or AIDS-related complex (Klecker et al 1988). The present study characterized the pharmacokinetics of DDC after administration to rats. Fig. 3 illustrates plasma DDC concentrations, normalized for dose per body weight, as a function of time for the five species. These pharmacokinetic profiles are noticeably different with lower dose normalized DDC concentrations in smaller species. Pharmacokinetic parameters following DDC administration to the various species are shown in Table 2. Total clearance and steady state volume of distribution values show a general increase with species body weight. The fraction of drug excreted in urine, however, is relatively consistent among the various species. Interestingly, half life is also virtually identical in all species. This results from a similar magnitude in variations in CL_T and V_{ss} with variations in species weight. Thus, although plasma DDC concentration-time profiles are different in each species, there are similarities in the general disposition of the drug.

Table 2. Pharmacokinetic parameters following administration of DDC to mice, rats, cats, monkeys and patients.

	Species				
Parameter	Mouse	Rat	Cat	Monkey	Man
W, kg	0·022	0·35	4·6	6·8	70·0
CL_T, L h^{-1}	0·033	0·53	4·8	3·1	26·6
V_{ss}, L	0·013	0·54	7·0	5·9	37·8
fe	0·64	0·49	—	0·68	0·75
CL_R, L h^{-1}	0·021	0·26	—	2·1	20·0
CL_{NR}, L h^{-1}	0·012	0·27	—	1·0	6·6
$t_{\frac{1}{2}}$, h	1·5	1·0	1·2	1·8	1·2

Results from this study were combined with pharmacokinetic data for DDC in mice, monkeys, cats and patients to develop a basis for interspecies scale-up of the disposition characteristics of the drug. Allometric relationships were sought between pharmacokinetic parameters (Table 2) and species body weight. Interspecies correlations for CL_T and V_{ss} are illustrated in Fig. 4. Both of these correlations were statistically significant ($r > 0·985$, $P < 0·01$) suggesting that interspecies scaling of DDC plasma concentrations was possible. The exponent of the interspecies correlation for V_{ss} (Fig. 4B) is essentially unity ($b = 0·99$) indicating that this parameter is a constant fraction of body weight independent of species or species size. In addition, since this exponent is unity an elementary Dedrick plot (Boxenbaum 1982) can be employed for interspecies scaling of plasma concentrations. Thus, for interspecies scale-up the concentration axis is simply normalized for dose per body weight. Total clearance

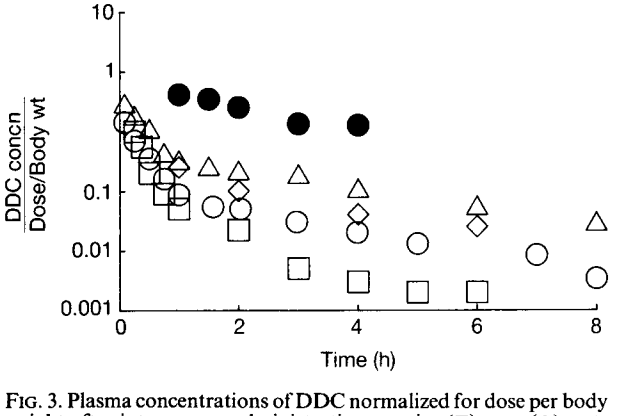

FIG. 3. Plasma concentrations of DDC normalized for dose per body weight after intravenous administration to mice (□), rats (○), cats (◇), monkeys (△) patients (●).

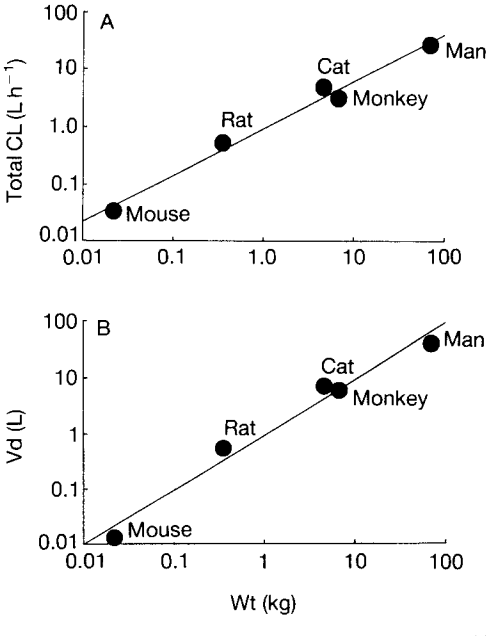

FIG. 4. Interspecies correlation between total clearance (A) and steady state volume of distribution (B) and species body weight. Regression lines for both figures were statistically significant: (A) $r = 0·992$, $P < 0·001$ (B) $r = 0·987$, $P < 0·01$.

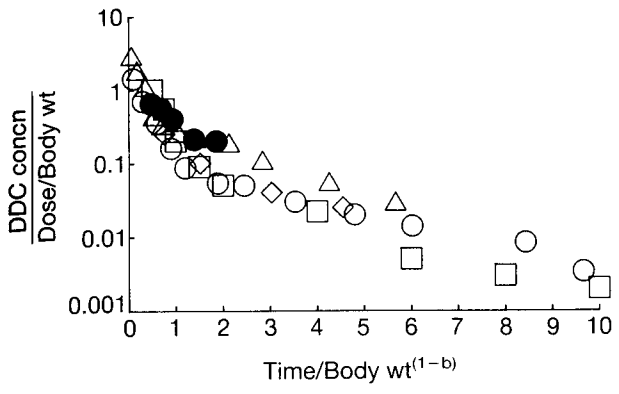

FIG. 5. Plasma concentrations of DDC in mice (□), rats (○), cats (◇), monkeys (△) and patients (●) scaled-up according to the elementary Dedrick plot. The time axis is divided by $W^{(1-b)}$ where $b=0{\cdot}82$. The concentration axis is normalized for dose per species body weight.

is described by the equation of simple allometry with an exponent b of 0·82. Chronologic time, then, needs to be scaled by dividing time by $W^{(1-0{\cdot}82)}$ or $W^{0{\cdot}18}$ (Boxenbaum 1982). Fig. 5 illustrates an elementary Dedrick plot using the data shown in Fig. 3. Transformation of these data using allometric relationships result in superimposable plasma DDC concentration-time profiles.

Renal clearance is a major route of elimination of DDC. Fig. 6A demonstrates a significant relationship between CL_R and species body weight. The exponent of this relationship is identical to that found for CL_T illustrating that the fraction of drug excreted in the urine is similar in each species. Indeed, renal clearance in rats and man is three-fold greater than glomerular filtration rate in each species. Active renal

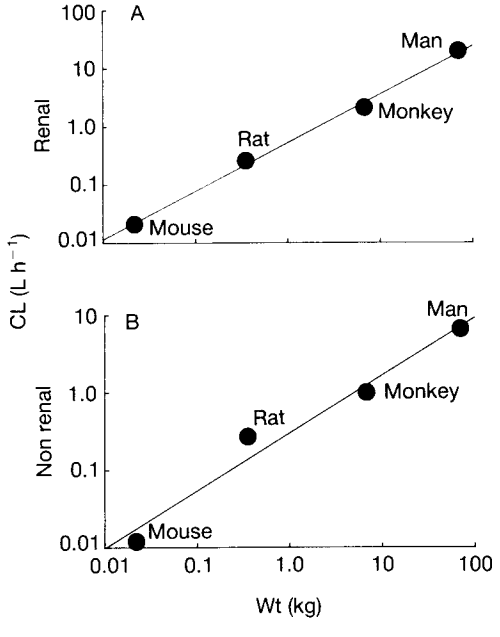

FIG. 6. Interspecies correlation between renal clearance (A) and nonrenal clearance (B) and species body weight. The regression lines were statistically significant: (A) $r=0{\cdot}998$, $P<0{\cdot}01$ (B) $r=0{\cdot}991$, $P<0{\cdot}01$.

tubular secretion is an important mechanism involved in the renal excretion of DDC in rats and man. Thus, mechanistic studies in rats examining drug elimination can be extrapolated to the clinical situation. A similar interspecies correlation observed for non-renal clearance is shown in Fig. 6B.

Interspecies scaling resulted in superimposable plasma DDC concentration-time curves from four laboratory animals and man. Significant interspecies correlations were found for total clearance, renal clearance, nonrenal clearance and steady state volume of distribution. These results demonstrate that pharmacokinetic results obtained in laboratory animals can be used to predict plasma DDC concentrations in man. Animal models examining the effects of altered physiological states and drug interactions, thus, can be used to predict changes in DDC pharmacokinetics in humans.

The disposition of DDC in rats is linear over a wide dosage range. Although doses administered to rats were large compared with those given to patients, results from the rat studies could be scaled-up to predict DDC concentrations in man. Similarities in mechanisms of drug distribution and elimination are also evident. Thus, the rat appears to provide an ideal animal model for further studies examining DDC pharmacokinetics.

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