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Pharmacokinetics of NS-49, a phenethylamine class α_{1A}-adrenoceptor agonist, at therapeutic doses in several animal species and interspecies scaling of its pharmacokinetic parameters

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Abstract

The pharmacokinetics of NS-49, a newly developed phenethylamine class α_{1A}-adrenoceptor agonist, was investigated in rats, rabbits, and dogs given intravenous and oral doses that have little effect on the renal blood flow rate (approximating the range of clinical doses). A three-compartment open model adequately described the plasma NS-49 profiles with respective elimination half-lives of 18, 19, and 13 h after intravenous administration of NS-49 to rats, rabbits and dogs. After oral administration, the NS-49 plasma concentrations reached their maximums within 1.5 h in all the species tested, then decreased as in intravenous administration. The systemic availability was 80% for the rats, 70% for the rabbits, and 101% for the dogs. From the pharmacokinetic parameter values for these three species, we predicted human pharmacokinetics of NS-49 after oral administration with an animal scale-up approach. The area under the plasma concentration-time curve (AUC) after oral administration, as well as the total body clearance showed an excellent allometric relationship to body weight across the three species. The oral AUC value for humans therefore could be predicted from this correlation. The predicted value agreed well with the observed value in the clinical phase I study. It was difficult to predict the plasma concentration profile of NS-49 for humans after oral administration because the absorption rate constant (k_a) that is essential for estimation of the maximum concentration exhibited no correlation across the species tested. But we approximately could simulate the plasma concentration profile of NS-49 for humans by using the k_a value for the rats or rabbits.

Keywords: α_{1A}-Adrenoceptor agonist; NS-49; Pharmacokinetics; Interspecies scaling

1. Introduction

NS-49, (R)-(−)-3′-(2-amino-1-hydroxyethyl)-4′-fluoromethanesulfonanilide hydrochloride, a newly developed phenethylamine class α_{1A}-

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adrenoceptor agonist (Obita et al., 1995; Muramatsu et al., 1995; Taniguchi et al., 1997), increases intraurethral pressure with little effect on blood pressure (Taniguchi et al., 1996). It therefore should be useful for treating stress incontinence. Pharmacokinetic studies with ^{14}C-NS-49 showed that it is well absorbed with essentially no first-pass metabolism and is eliminated mainly by renal excretion in rats, rabbits, and dogs, but not in monkeys (Mukai et al., 1999(a), 1999(b)). In those studies, we could not adequately evaluate the systemic availability for rabbits and dogs from the plasma concentration of NS-49 because renal clearance, which accounts for most of the total clearance, decreased after intravenous injection. Reduction in the renal clearance value is considered to be due to the decrease in the renal blood flow rate caused by the α_1-adrenergic stimulating action of NS-49 because the test doses were ten- to 100-fold the therapeutic doses. We therefore investigated the pharmacokinetics of NS-49 in various animal species after administration of doses that have little effect on the renal blood flow rate. We also did interspecies scaling of the pharmacokinetic parameters of NS-49 in order to predict the plasma concentration in humans.

2. Materials and methods

2.1. Compounds and reagents

NS-49 and d_3, ^{13}C-NS-49, the internal standard, were synthesized in our laboratories. Their chemical structures are shown in Fig. 1. Pentafluoropropionyl imidazole (PFPI) and tert-butyl-dimethylsilyl imidazole (t-BDMSI) were purchased, respectively, from GL Science (Tokyo, Japan) and Tokyo Chemical Industry (Tokyo, Japan). Ethyl acetate, n-hexane, and benzene were of HPLC grade. All the other reagents used were of guaranteed reagent grade.

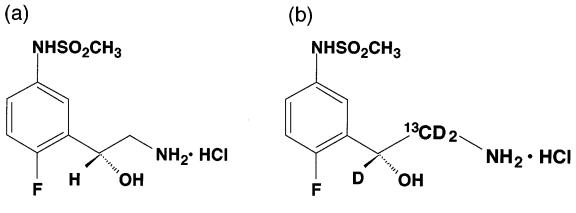

Fig. 1. Chemical structures of NS-49 (a); and d_3, ^{13}C-NS-49 (b).

2.2. Animals

Male Sprague–Dawley rats (7–8 weeks; Slc, Japan SLC, Hamamatsu, Japan), male rabbits (3–4 kg; Kbs:JW, Kitayama Labes, Nagano, Japan), and male Beagle dogs (9–12 kg; Laboratory Research Enterprise, Kalamazoo, MI, USA) were used. Before testing, the animals were acclimated to conditions of 23 ± 2°C and 55 ± 5% relative humidity; rats for at least a week, rabbits for 2 weeks, and dogs for 3 weeks. Water and pellet food (rats, F-2, Funabashi Farms, Funabashi, Japan; rabbits, RC4, Oriental Yeast, Tokyo, Japan; dogs, TC-1, Taiyo Pet Food, Tokyo, Japan) were available ad libitum. Food was withdrawn for 24 h before the tests were done.

2.3. Drug preparation and dose

NS-49 was dissolved in saline for intravenous injection or in a 0.5% aqueous solution of methyl cellulose for oral administration. The intravenous injection was to the jugular veins of the rats (0.02 mg/2 ml per kg), the marginal ear veins of the rabbits (0.02 mg/ml per kg), and the cephalic veins of the dogs (0.01 mg/ml per kg). Oral administration of the same doses was given through a stomach tube.

2.4. Determination of the plasma concentration

At designated times after the intravenous or oral administration of NS-49, blood samples were drawn into heparinized test tubes from the jugular veins of the rats, marginal ear veins or hearts of the rabbits, and cephalic veins of the dogs. Plasma was obtained after centrifugation (3000 rpm for 10 min) of these samples. Portions (0.2–1.0 ml) of the plasma samples combined with 0.5 ml of 0.05 M phosphate buffer (pH 7.0) and 25 μl of the

internal standard solution (I.S.; d_3, ^{13}C-NS-49, 0.1 μg/ml) were applied to Bond Elut Certify cartridges (Varian, Harbor City, CA, USA) conditioned prior to use by passing 2 ml of methanol and 5 ml of phosphate buffer through them. The cartridges were washed with 2 ml of phosphate buffer and 2 ml of methanol, then NS-49 was eluted with 2 ml of 2.8% ammonium hydroxide in methanol. The eluates were dried under reduced pressure at room temperature, then 100 μl of 5% PFPI in ethyl acetate was added to each dried residue, after which the samples were heated at 70°C for 20 min. The solvent was evaporated under reduced pressure at room temperature. Fifty microliters of 10% t-BDMSI in pyridine was added to each residue, after which the samples were heated at 70°C for 30 min. After cooling, the solvent was diluted with 1 ml of water and stirred briefly. The resulting derivatives were extracted with 5 ml of benzene. The organic layer was separated and dried in vacuo at 40°C. The residues were dissolved in 25 μl of ethyl acetate, then a portion (1–2 μl) was injected to a gas chromatograph-mass spectrometer (GC/MS) (Hitachi M-2500 equipped with a Hitachi G-3000 gas chromatograph, Hitachi, Tokyo, Japan), and separated in a 30 m × 0.32 mm DB-5 ms capillary column (J & W Scientific, Folsom, CA, USA) with a 0.25-μm film thickness. The column was connected to the injector by a deactivated uncoated capillary column (2 m × 0.32 mm, J & W Scientific) as a retention gap, and the outlet was passed through the mass spectrometer interface directly to the ion source. Helium was the carrier gas at the flow rate of 1.5 ml/min. Injection was made in the splitless mode at 290°C, and the injector purge opened after 0.5 min at the split ratio of 80:1. The column temperature was programmed for a 0.5-min hold at 200°C, followed by heating to 300°C at 30°C/min. The mass spectrometer was operated in the EI mode with an electron energy of 70 eV and emission current of 80 μA. The GC/MS interface was maintained at 250°C, and the ion source temperature at 200°C. Selected ion monitoring used the ions at m/z 451 and 455.

2.5. Pharmacokinetic analysis

2.5.1. Calculation of pharmacokinetic parameters

Parameter estimation was accomplished using the non-linear least-squares regression analysis program MULTI (Yamaoka et al., 1981). The inverse value of each data point was used as the weighting value in the least-squares method. A three-compartment open model was fitted to the mean plasma concentrations of NS-49 for rats or to the individual plasma concentrations of NS-49 for rabbits and dogs. The maximum plasma concentration (C_{max}), time (T_{max}) at which C_{max} occurred, elimination half-life ($t_{1/2\ \beta}$), apparent volume of distribution at steady state (V_{ss}) and area under the plasma concentration-time curve ($AUC_{0-\infty}$) were derived from the model-dependent parameters. Total body clearance (CL_{tot}) for the intravenous administration was determined from the $Dose/AUC_{0-\infty}$.

2.5.2. Interspecies scaling of the pharmacokinetic parameters

Allometric relationships between various pharmacokinetic parameters (P) and body weight (W) were plotted on a log–log scale. The linear regression of the logarithmic values was calculated by the least-squares method using Eq. (1) to obtain the coefficient (α) and exponent (β) values (Boxenbaum, 1984):

$$P = \alpha \times W^{\beta} \tag{1}$$

The plasma concentration profile after oral administration of NS-49 to humans is predicted by Eq. (2):

$$C_{po} = [(F \times \text{Dose} \times k_a)/(V_1 \times (k_a - CL_{tot}/V_1))] \times [\exp(-CL_{tot} \times t/V_1) - \exp(-k_a \times t)] \tag{2}$$

where C_{po} is the plasma concentration; k_a is the absorption rate constant; CL_{tot} is the total clearance; V_1 is the volume of distribution; F is the bioavailability; and t is the time after administration.

The predicted values for humans were compared with the plasma concentrations of NS-49 observed in a phase 1 study with NS-49 tablets. In

the phase 1 study, 17 healthy male volunteers, aged 24–45 years, were selected. The volunteers were instructed to abstain from taking any medication for 1 week prior to and during the study period. The drug (0.8 mg) was administered orally to six volunteers (aged 25–39 years) in fasting state with 100 ml of water. Blood samples (5 ml) were drawn at 0, 0.5, 1, 2, 3, 4, 6, 8, 12 and 24 h. The blood samples were centrifuged immediately to obtain plasma. The plasma samples were assayed for NS-49 concentrations with a sensitive and specific GC/MS method as described above.

3. Results

3.1. Plasma concentration of NS-49

The plasma concentrations of NS-49 after a single intravenous or oral administration are shown in Fig. 2, and the pharmacokinetic parameter values in Table 1. After intravenous administration to the rats, rabbits and dogs, the plasma concentrations of NS-49 decreased triexponentially with respective $t_{1/2\,\beta}$ values of 18, 19 and 13 h. The CL_{tot} value per kilogram of body weight was higher in the smaller animal; rat (1.45 l/h per kg) > rabbit (0.47 l/h per kg) > dog (0.39 l/h per kg). After oral administration, the plasma concentrations of NS-49 reached maximums within 1.5 h in all the species tested, then decreased as in the intravenous injection. The $AUC_{0-\infty}$ values were 11.1 ng × h/ml for the rats, 34.7 ng × h/ml for the rabbits, and 28.0 ng × h/ml for the dogs, the dose-normalized values increasing with species size. Systemic availability (F) was high in all three species; rats 80%, rabbits 70%, and dogs 101%.

3.2. Interspecies scaling of the pharmacokinetic parameter values

The CL_{tot} of NS-49 calculated after intravenous administration showed a good allometric relationship to body weight across the rats, rabbits, and dogs (Fig. 3). The correlation was characterized by $CL_{tot} = 13.6 \times W^{0.640}$ ($r = 0.995$).

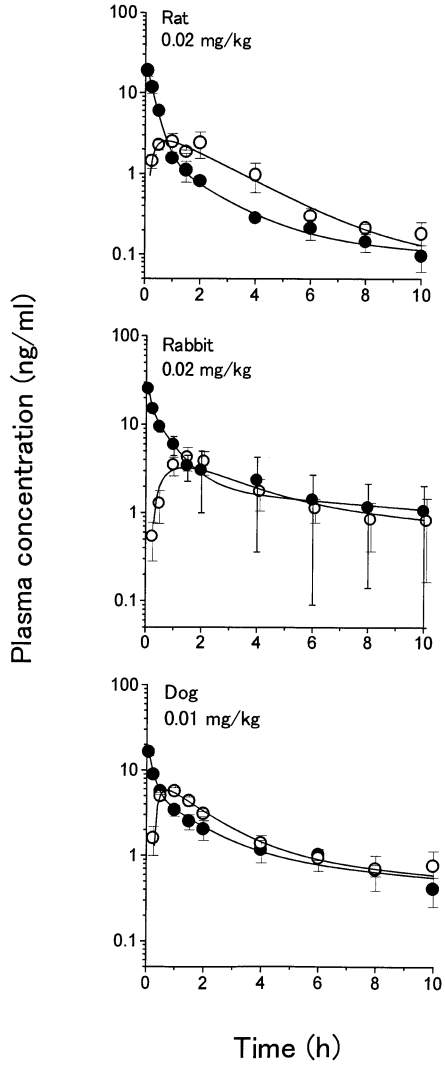

Fig. 2. Plasma concentrations of NS-49 after intravenous and oral administrations of NS-49 to rats, rabbits and dogs. ●, intravenous; ○, oral. Curves show the model-predicted values. Each point represents a mean ± S.D. ($n = 3$).

This result suggests that the $AUC_{0-\infty}$ value after oral administration, which is calculated by Dose × F/CL_{tot}, also is allometrically scaled to body weight across the three species because there are no marked species-differences in the F value (Table 1). We therefore did interspecies scaling of the dose-normalized $AUC_{0-24\ h}$ value after oral administration to investigate whether the human pharmacokinetics of NS-49 conforms to the corre-

lation across the three other animal species, because the $AUC_{0-24\ h}$ value had been determined in the phase 1 study. As a result, there was a good allometric relationship between the oral $AUC_{0\text{-}24\ h}$ value and body weight across the rats, rabbits, and dogs (Fig. 4; $AUC_{0-24\ h}/Dose = 0.958 \times W^{0.376}$; $r = 0.994$). Then the human $AUC_{0-24\ h}$ value that was obtained in the phase 1 study almost conformed to the correlation.

3.3. Prediction of the plasma concentration profile of NS-49 for humans after oral administration

The human plasma concentration profile of NS-49 observed in the phase 1 study can be described by one-compartment open model (Eq. (2)). We assumed the human F value to be unity because this drug is well absorbed with essentially no first pass metabolism in all the animal species investigated. We can estimate the human CL_{tot} value from the allometric relationship shown in Fig. 3. For the calculation with Eq. (2) we further must estimate the human V_1 and k_a values. To estimate these two parameters for humans, we cannot use the values for other species shown in Table 1 because those values were calculated from the different pharmacokinetic model (i.e. three-compartment model). Therefore the V_1 and k_a values for rats, rabbits, and dogs were obtained by fitting the one-compartment model equation to the plasma concentrations within 8 h after oral administration. The estimated values for V_1 and k_a based on the one-compartment model are shown in Table 2. The V_1 values showed a good allometric relationship to body weight (Fig. 5), and the human V_1 value could be estimated. Evaluation of the k_a value for humans, however, was difficult because there was no k_a value correlation across the species tested; rat (0.727 h^{-1}), rabbit (0.595 h^{-1}), dog (2.17 h^{-1}). We therefore predicted the human plasma concentration profile by using low (0.6 h^{-1}; being close to the value for rats or rabbits) or high (2.0 h^{-1}; being close to the value for dogs) k_a values. As a result, the human plasma

Table 1
Pharmacokinetic parameter values of NS-49 after intravenous and oral administrations to rats, rabbits and dogs

Route	Parameter	Rat ($n = 3$)	Rabbit[a] ($n = 3$)	Dog[a] ($n = 3$)
i.v.	Dose (mg/kg)	0.02	0.02	0.01
	P (ng/ml)[b]	24.1	24.2 ± 3.2	17.0 ± 3.3
	A (ng/ml)[b]	1.88	12.8 ± 8.3	4.58 ± 1.63
	B (ng/ml)[b]	0.158	1.30 ± 0.96	0.982 ± 0.392
	π (h^{-1})[b]	3.76	9.88 ± 5.88	5.74 ± 1.63
	α (h^{-1})[b]	0.587	0.942 ± 0.629	0.665 ± 0.295
	β (h^{-1})[b]	0.0377	0.0380 ± 0.0086	0.0612 ± 0.0332
	V_1 (l/kg)[b]	0.764	0.533 ± 0.096	0.447 ± 0.054
	V_{ss} (l/kg)[c]	12.4	6.87 ± 1.46	4.39 ± 1.24
	$t_{1/2,\ \beta}$ (h)[c]	18.4	19.0 ± 5.0	13.4 ± 5.7
	$AUC_{0-\infty}$ (ng × h/ml)[c]	13.8	58.1 ± 43.7	27.9 ± 9.9
	CL_{tot} (l/h per kg)[c]	1.45	0.468 ± 0.248	0.385 ± 0.114
p.o.	Dose (mg/kg)	0.02	0.02	0.01
	k_a (h^{-1})[b]	0.581	0.543 ± 0.179	1.87 ± 0.38
	T_{lag} (h)[b]	0.0893	0.217 ± 0.014	0.249 ± 0.090
	C_{max} (ng/ml)[c]	2.55	3.22 ± 0.74	5.86 ± 0.83
	T_{max} (h)[c]	0.900	1.46 ± 0.28	0.710 ± 0.029
	$AUC_{0-\infty}$ (ng × h/ml)[c]	11.1	34.7 ± 14.0	28.0 ± 8.9
	F[b]	0.802	0.700 ± 0.222	1.01 ± 0.05

[a] Each parameter value is a mean ± S.D.
[b] Estimated by non-linear least squares fitting of three-compartment model equations to the mean (rat) or individual (rabbit and dog) plasma concentrations of NS-49.
[c] Calculated from the model-dependent parameters.

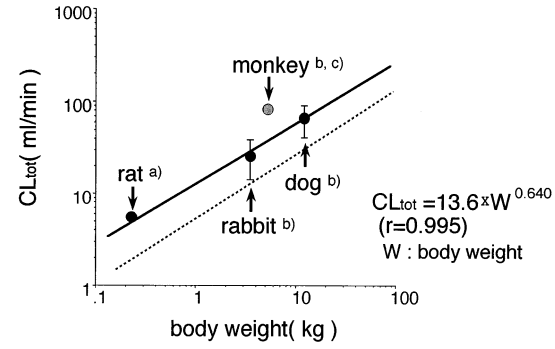

Fig. 3. Allometric relationship between CL_{tot} and body weight. The solid line was calculated by the least squares method using unweighted logarithmically transformed data for the rats, rabbits and dogs. The dotted line shows the correlation between GFR and body weight; $GFR = 5.92 \times W^{0.77}$ (Sawada, 1985). [a]Derived from the mean plasma concentration for three animals. [b]Mean ± S.D. for three individual values. [c]Data from Mukai et al. (1999).

concentration profile observed in the phase 1 study was approximately simulated with the k_a value of 0.6 h^{-1} (Fig. 6).

4. Discussion

We investigated the pharmacokinetics of NS-49 in rats, rabbits, and dogs after intravenous and oral administrations of doses that have little effect on the renal blood flow rate (approximating the range of clinical doses). The systemic availability

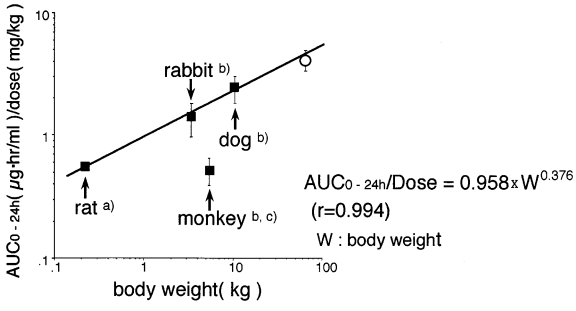

Fig. 4. Allometric relationship between $AUC_{0-24\ h}$ and body weight after oral administration of NS-49. The solid line was calculated by the least squares method with unweighted logarithmically transformed data for the rats, rabbits, and dogs. ○: observed value for humans in the phase 1 study. See legend to Fig. 3 for key.

Table 2
Pharmacokinetic parameter values of NS-49 for rats, rabbits, and dogs estimated by fitting the one-compartment model equation

	Rat	Rabbit[a]	Dog[a]
V_1 (l)[b]	0.979	7.70 ± 1.74	16.4 ± 3.9
k_a (h^{-1})[b]	0.727	0.595 ± 0.310	2.17 ± 0.37

[a] Each parameter value is a mean ± S.D. ($n = 3$).
[b] Estimated by non-linear least squares fitting of one-compartment model equation to the mean (rat) or individual (rabbit and dog) plasma concentrations of NS-49.

was 80% for the rats, 70% for the rabbits, and 101% for the dogs, values almost the same as those found for urinary-excreted NS-49 in previous studies with ^{14}C-NS-49 (Mukai et al., 1999(a), 1999(b)). These findings confirm that intravenous injection of NS-49 at a therapeutic dose does not reduce the renal blood flow rate and that the pharmacokinetic parameter values obtained in this study accurately describe the disposition characteristics of NS-49.

To investigate whether the pharmacokinetics of NS-49 for humans can be predicted from animal data, we did interspecies scaling of the pharmacokinetic parameter values across the species (rats, rabbits and dogs) tested. The drug, known to be eliminated mainly by renal excretion, shows a good allometric relationship between CL_{tot} and

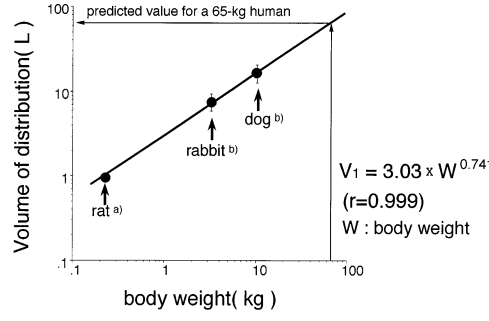

Fig. 5. Allometric relationship between NS-49 distribution volume (V_1) and body weight. The values for rats, rabbits, and dogs were obtained by fitting the one-compartment open model to the plasma NS-49 concentrations within 8 h after administration. The solid line was calculated by the least squares method with unweighted logarithmically transformed data. See legend to Fig. 3 for key.

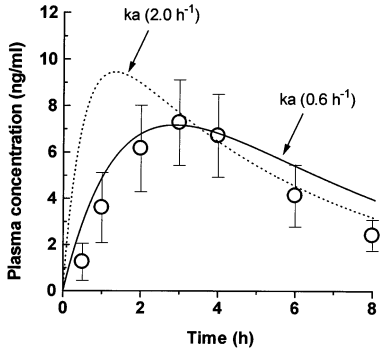

Fig. 6. Simulated and observed plasma concentration profiles of NS-49 after oral administration of 0.8 mg to healthy male volunteers. Each point represents the mean value ($n = 6$) obtained in the phase I study (unpublished data). The solid lines, calculated using Eq. (2), represent estimated values for $k_a =$ 0.6 and 2.0 h^{-1}.

body weight across various animal species, except where there are species differences in plasma protein binding (Cherkofsky, 1995). NS-49 is eliminated mainly via renal excretion, and CL_{re} accounts for most of CL_{tot}; in rats, rabbits and dogs (Mukai et al., 1999(a), 1999(b)). Furthermore, there were no marked differences in the serum protein binding of NS-49 in these animal species (Mukai et al., 1999(a), 1999(b)). CL_{tot} therefore correlated well with body weight across the rats, rabbits, and dogs (Fig. 3). The difference between CL_{tot} and gromerular filtration rate (GFR) in Fig. 3 gives the renal tubular secretion rate of NS-49. The slope of the regression line for CL_{tot} approximated that for GFR, indicative that the ability to secrete NS-49 via renal tubules also correlates well with body weight. Several β-lactam antibiotics, mainly eliminated by renal excretion via tubular secretion, show good allometric relationships between CL_{re} corrected for the serum unbound fraction and body weight (Sawada et al., 1984; Matsushita et al., 1990). Furthermore, the allometric exponents of the correlations, 0.7–0.8, agree with those in the allometric analysis of such physiological parameters of the kidney as organ mass, number of nephrons, and surface area of the renal tubules. It therefore is considered that there are no marked species differences in the ability to secrete β-lactams in a certain surface area of the renal tubules. This is supported in NS-49 because the allometric exponent of about 0.7 characterizes the relationship between CL_{tot} and body weight.

Elsewhere we showed that NS-49 is metabolized extensively only in monkeys, about half the CL_{tot} for monkeys being due to non-renal clearance (Mukai et al., 1999(a), 1999(b)). The observed CL_{tot} and AUC values for monkeys therefore deviated from the regression line obtained across rats, rabbits and dogs (Figs. 3 and 4).

Most interspecies scaling studies have been restricted to the prediction of pharmacokinetics after intravenous administration, rather than after the more common oral route, because of species differences in bioavailability. As there were no marked species differences in the bioavailability of NS-49, the pharmacokinetic parameters of NS-49 after oral administration were considered to show good allometric relationships to body weight. We did interspecies scaling of the AUC value from 0 to 24 h ($AUC_{0-24\ h}$) after oral administration to the test species because the AUC value for humans had been determined over a 24-h period post administration in the phase I study. There was a good allometric relationship between the oral $AUC_{0-24\ h}$ value and body weight across the rats, rabbits and dogs (Fig. 4). The $AUC_{0-24\ h}$ value after oral administration of 0.8 mg of NS-49 to a 65-kg human was estimated from this correlation to be 57 ng × h/ml, a value very close to the observed one, 51 ng × h/ml, in the phase I study. These results indicate that this methodology can be used to predict the oral AUC value of NS-49 for humans.

Lastly, we attempted to predict the plasma concentration profile of NS-49 for humans after oral administration. The plasma concentrations observed in the phase 1 study were not sufficient for evaluation of the elimination phase, and then we used the one-compartment open model (Eq. (2)) to predict the human plasma concentration profile. We assumed the human F value to be unity. For a 65-kg human, the CL_{tot} value was estimated to be 11.8 l/h from the allometric relationship that is shown in Fig. 3. After the V_1 and k_a values for rats, rabbits, and dogs were calcu-

lated from the one-compartment model analysis, the human V_1 value was estimated to be 67 l. But the evaluation of the k_a value for humans was difficult because there was no k_a value correlation across the species tested; rat (0.727 h^{-1}), rabbit (0.595 h^{-1}), and dog (2.17 h^{-1}). We fortunately could approximately simulate the human plasma concentration profile of NS-49 by using the k_a value for rats and rabbits, namely 0.6 h^{-1}. To predict the human plasma concentration profile precisely, a method that accurately estimates the k_a value for humans is required.

In conclusion, NS-49 was well absorbed with no appreciable first-pass metabolism and provided high bioavailability in rats, rabbits and dogs. Using allometric scaling techniques applied to the pharmacokinetic parameter values of NS-49 for these animal species, we could predict the human AUC value after oral administration of NS-49. To simulate the human plasma concentration profile of NS-49, however, a method that accurately estimates the k_a value for humans is required.

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