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Pharmacokinetics and interspecies scaling of a novel VEGF receptor inhibitor, SU5416

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Abstract

The pharmacokinetics and allometric relationships of SU5416, a novel small anti-angiogenesis agent, were studied. The pharmacokinetics of SU5416 were examined in mice, rats, dogs, and cancer patients. The in-vitro intrinsic clearance (CL_{int}) was estimated from the in-vitro metabolism study in mouse, rat, dog, monkey and human liver microsomes. The parameters of interest were correlated across species as a function of bodyweight using an allometric approach. The steady-state volume of distribution (Vd_{ss}), plasma clearance (CL_s), and CL_{int} of SU5416 were well correlated across species. The exponent of the allometric relationship (b) of the corresponding parameters was 0.92, 0.80 and 0.66, respectively. The elimination half-life ($t_{\frac{1}{2}}$) was consistent across species and independent of bodyweight. The prediction of CL_s, Vd_{ss}, CL_{int}, and $t_{\frac{1}{2}}$ in humans using the data from mouse, rat, and dog, and monkey (for CL_{int}) was reasonably good (within 4-fold of the observed values). However, an improved prediction (within 2-fold of the observed values) of the corresponding parameters in humans was obtained when extrapolation from only the rodent data was performed, suggesting that the rodent data are sufficient for the scale-up of SU5416 pharmacokinetic parameters in humans. Using allometry, it was possible to achieve reasonable predictions of the pharmacokinetic parameters of SU5416 in cancer patients with various solid tumours.

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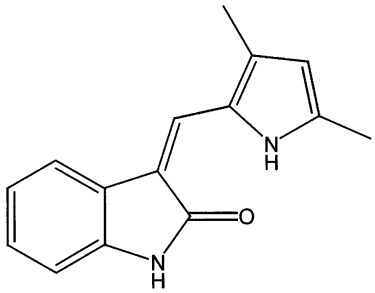
Introduction

Angiogenesis is defined as the sprouting of new vessels from existing vasculature, which is an essential process in the growth of solid tumours. Vascular endothelial growth factor (VEGF) and its receptors (Flk-1) have been implicated in angiogenesis that occurs in many solid tumours (Strawn et al 1996; Shawver et al 1997). SU5416, 3-[(2,4-dimethylpyrrol-5-yl)methylidenyl]-indolin-2-one, is a synthetic small polar aromatic molecule (Figure 1) developed as a potent and specific inhibitor of the VEGF receptor tyrosine kinase, Flk-1/KDR (fetal liver kinase-1/kinase insert domain-containing receptor). In a tumour xenograft model in mice, the compound has been shown to have anti-angiogenic properties and inhibits neovascularization of tumours, which thereby halts tumour growth (Fong et al 1999; Mendel et al 2000). SU5416 is a selective inhibitor of VEGF receptor function, currently in phase III clinical trials for the treatment of metastatic colorectal cancer. Phase I and II studies of SU5416 have been completed in a wide variety of tumour patients and the results have shown that SU5416 is well tolerated for chronic administration with indications of biological activity (Cropp et al 1999; Rosen et al 1999).



SU5416

Figure 1 Chemical structure of SU5416.

SU5416 acts selectively through inhibition of the Flk-1/KDR receptor on the endothelial cells and does not directly inhibit the growth of cells of solid tumour origin. In biochemical assays utilizing recombinant receptor tyrosine kinase proteins, SU5416 is a potent and selective competitive (with respect to ATP) inhibitor of Flk-1/KDR with a K_i value of 0.16 μM (Mendel et al 2000). In a cell-based assay, SU5416 selectively inhibits the KDR-mediated VEGF-dependent mitogenic response of human umbilical endothelial cells with an IC50 value of 0.04 μM (Fong et al 1999). Vajkoczy et al (1999) studied the anti-angiogenic properties of SU5416 in-vivo using intravital multi-fluorescence video-microscopy and found that SU5416 treatment caused a reduction in the permeability and in the total and functional vascular density of the newly formed tumour microvasculature of tumour-bearing mice. Consistent with its in-vitro effects on endothelial cells and anti-angiogenic effects in-vivo, SU5416 inhibited the growth of tumours in a variety of mouse xenograft models (Fong et al 1999; Mendel et al 2000). As shown by Mendel et al (2000), SU5416 treatment (daily intraperitoneal administration of 3–25 mg kg^{-1}) caused dose-dependent inhibition of the subcutaneous growth of A375 human melanoma cells in athymic mice.

In preclinical species, SU5416 was rapidly cleared from the plasma in-vivo. The total systemic clearance of the compound was high and primarily through hepatic metabolism. To understand the metabolism of the compound, in-vitro biotransformation of SU5416 was studied in mouse, rat, dog, monkey and human liver microsomes (Antonian et al 2000). The compound was rapidly metabolized in liver microsomes and was primarily converted to a hydroxy metabolite predominantly through hydroxylation of the 5′-methyl group on the pyrrole ring, which was further transformed to a corresponding carboxylic acid. Both of these oxidative products are further metabolized in-vivo through glucuronidation.

Interspecies scaling, the prediction of human exposure to drugs based on data from preclinical species, is a useful tool in the process of drug development. Allometric scaling is a method of interpolation and extrapolation based on the principle that physiological parameters among mammalian species can be related to their bodyweight. This approach has been successfully applied in the interspecies scaling of both in-vivo pharmacokinetic parameters and in-vitro data (i.e. intrinsic clearance) for various types of compounds (Brocks et al 1996; Lave et al 1996; Mahmood 1998; Lin et al 1999). The aims of the present study were to examine the pharmacokinetics of the novel angiogenesis inhibitor SU5416, to study the allometric relationship of pharmacokinetic parameters and in-vitro intrinsic clearance (CL_{int}) of the compound across species, and to evaluate the feasibility of extrapolation of those parameters from animals to humans using an allometric approach.

Methods

Pharmacokinetic studies

Preclinical pharmacokinetics of SU5416 were determined in female nu/nu mice, male Sprague-Dawley rats and female beagle dogs after intravenous administration. Nu/nu mice are athymic and immunodeficient. Female mice were used as an animal model to study the efficacy and pharmacokinetics of SU5416. There were no gender differences in the disposition kinetics of SU5416 (data not shown), therefore male Sprague-Dawley rats and female beagle dogs were used in this study. Double cannulated (jugular vein and carotid artery) rats were obtained from Charles River Laboratories (Hollister, CA). The pharmacokinetics of SU5416 in humans ($n = 69$) were obtained during a phase I dose-escalating study in cancer patients with advanced malignancies (Cropp et al 1999). The investigations in humans were performed after approval by the Institutional Review Board. The animal experimentation was conducted in accordance with the ILAR Guide for the Care and Use of Laboratory Animals and with SUGEN Animals Care and Use Committee guidelines.

SU5416 reference standard (purity 99.8%) was obtained from the Chemistry Department, SUGEN, Inc, CA, USA. Owing to limited aqueous solubility, SU5416 was administered in a Cremophor-based formulation. Cremophor, polyoxyl 35 castor oil, is a surfactant that provides maximum aqueous solubility for SU5416. As dogs are known to be hypersensitive to Cremophor as a

result of histamine release, Solutol was used in place of Cremophor for studies in dogs.

In mice (20–24 g), SU5416 was administered as a bolus intravenous injection (5 mL kg^{-1}) via the tail-vein at 16.7 mg kg^{-1} (50 mg m^{-2}). Blood samples were collected at different time-points up to 90 min after administration by cardiac puncture (n = 4 for each time-point). In rats (300–320 g, n = 4), SU5416 was administered as a short intravenous injection (4 mL kg^{-1} over 1 min) via a jugular vein catheter at 5 mg kg^{-1} (32.5 mg m^{-2}). Blood samples were collected at different time-points up to 240 min after administration via a carotid artery catheter. In dogs (8–12 kg, n = 6), SU5416 was administered as a short intravenous injection (1 mL kg^{-1} over 1 min) into the cephalic vein at 2 mg kg^{-1} (42 mg m^{-2}). Blood samples were collected at different time-points up to 24 h after administration via the jugular vein. The total volume of blood drawn was less than 20 % of the total blood volume in all species.

In cancer patients (mean body surface area = 1.8 m^2, n = 69 including males and females), SU5416 was administered at 11 different dose levels ranging from 4.4 to 190 mg m^{-2} (0.1–5.0 mg kg^{-1}) (Cropp et al 1999). The dose was administered either as a slow bolus injection (dose levels of 4.4–36 mg m^{-2}) or as an intravenous infusion at 200 mL h^{-1} (for dose levels greater than 36 mg m^{-2}). Blood samples were collected at different time-points up to 4 h after the administration of SU5416. At doses of 65 mg m^{-2} and greater, additional blood samples were drawn up to 24 h after infusion.

Plasma was prepared by centrifugation at 4°C for 10 min at 3500 rpm in a microfuge and stored at −80°C pending analysis. Plasma concentrations of SU5416 were determined by a reverse-phase high-performance liquid chromatography method with UV/visible detection.

Analytical procedures

SU5416 was separated from plasma by protein precipitation using acetonitrile. SU5614 (chloro-derivative of SU5416) was used as an internal standard. Precipitated protein was removed by centrifugation. Extracts were evaporated to dryness and reconstituted in methanol and analysed using an HPLC/UV assay. Samples were analysed using HP1090 with UV detection (Hewlett-Packard, Germany) equipped with a HP Hypersil ODS column (200 × 4.6 mm, 5 μm particle size; Hewlett-Packard, Germany) at 40°C. The gradient used was initially at 0 % methanol : buffer (35 mM KH_2PO_2, 0.1 % triethylamine, pH 6.5), increasing to 100 % methanol : buffer by 11 min at a flow-rate of 1.2 mL min^{-1}. Detection of SU5416 was carried out at 440 nm. The linear range of the assay was 10–2000 ng mL^{-1} and 25–10 000 ng mL^{-1} for the analysis of human and animal plasma, respectively. The limit of quantitation of the assay was 10 ng mL^{-1} (0.5 mL sample) and 25 ng mL^{-1} (0.2 mL sample) for the analysis of human and animal plasma, respectively. Five individual calibration curves were run to establish the precision and accuracy of the assay. A linear least-square regression analysis (weighted 1/x) of the concentrations of the calibration standards versus area ratios of SU5416 to the internal standard was constructed. The accuracy of the assay was within 98–102 %. The precision of the assay, determined as the coefficient of variation, was less than 10 %.

Pharmacokinetic data analysis

The pharmacokinetics of SU5416 in animals and humans were determined by compartmental analysis using WinNonlin-Pro (Version 2.1; Pharsight Corp., Mountain View, CA) and NONMEM V (Version 1.0; NONMEM Project Group, UCSF, San Francisco, CA), respectively. Data from individual animals or subjects were evaluated separately; however, mean concentrations were used for pharmacokinetic analysis in mice. The plasma concentration–time data were fitted to a two-compartmental model. A weighting of $1/C^2$ (where C is the observed concentration) was applied to optimize the data fitting in all species, except for dogs, where the uniformity of weight (unweighted) provided the best fit. The goodness-of-fit was determined by visual inspection of both the concentration–time profile and the plot of the residuals. The correlation of the observed and fitted data was greater than 0.82 in all species.

In-vitro metabolic rate of SU5416

The initial rate of disappearance of SU5416 was estimated using concentration–time data of the compound in the liver microsomal incubation at 37°C for 60 min obtained from Antonian et al (2000). In that study, in-vitro metabolism of 25 μM SU5416 was studied in mouse, rat, dog, monkey and human liver microsomes. Pooled liver microsomes from male CD-1 mice, athymic and immunodeficient mice, male Sprague-Dawley rats, male beagle dogs, male cynomolgus monkeys and humans were used.

CL_{int} was estimated from the rate of disappearance of SU5416 from microsomal incubations by Equations 1 and 2, where rate is the initial rate of disappearance of SU5416 in the liver microsomal incubation and [S] is the initial SU5416 concentration (Houston & Carlile 1997).

The protein concentration in the incubation was 0.5 mg and the amount of protein (g liver)$^{-1}$ was 15 mg. The liver weight for each species was obtained from the literature (Davies & Morris 1993).

$$CL_{int} = V_{max}/K_m \approx \text{rate}/[S] \quad (1)$$

$$CL_{int} = (\text{mL min}^{-1})/(0.5 \text{ mg protein}) \times (15 \text{ mg protein (g liver)}^{-1} \times (\text{g liver (kg bodyweight)}^{-1}) \quad (2)$$

In-vitro plasma protein binding

[^{14}C]SU5416 (specific activity = 13.56 mCi мм$^{-1}$, purity = 96.7%) was obtained from SynPep Corp. (Dublin, CA, USA). In-vitro plasma protein binding of [^{14}C]-SU5416 was determined in female nu/nu mouse, male Sprague-Dawley rat and healthy volunteers using an ultrafiltration device. Blood was collected into heparinized tubes. Plasma was separated and pooled for each species. The protein binding of [^{14}C]SU5416 as a function of concentration was studied over a concentration range that was observed in efficacy studies (0.06–8 μg mL^{-1} in mouse plasma) and in pharmacokinetic studies (0.06–4 μg mL^{-1} in rat and human plasma). Triplicate plasma samples at each concentration for each species were studied.

The non-specific binding of SU5416 to the Centrifree tube before ultrafiltration was determined by incubating the spiked plasma sample with [^{14}C]SU5416 in the ultrafiltration device with YMT membrane (Centrifree; Amicron Corp, Danvers, MA, USA) in a shaking water bath (Precision Scientific, Chicago, IL, USA) at 90 rev min^{-1} for 30 min at 37°C. The non-specific binding to the Centrifree tube before ultrafiltration $[(a_1 - a_2)/a_1]$ was determined from the difference of total radioactivity before (a_1) and after (a_2) incubation, divided by the total radioactivity before incubation (a_1). The Centrifree tube was then centrifuged at 37°C at 3500 rev min^{-1} (1500 *g*) for 30 min using a fixed-angle rotor centrifuge (Beckman model J2–21; Palo Alto, CA, USA). The radioactivity of an aliquot of the filtrate was determined (a_3).

The remaining filtrate from each cup was transferred to separate scintillation vials. The filtrate cup was washed with methanol (2 × 0.5 mL) and the washes were pooled to the respective vial containing the remaining filtrate and the total radioactivity was determined (a_4). For each empty, washed cup, the radioactivity (a_5) was also determined. The non-specific binding to the filtrate cup was determined by $[a_5/(a_3 + a_4 + a_5)]$. The actual radioactivity corrected for the non-specific binding of the free drug to the filtrate cup after ultrafiltration (a_6) was calculated by $[(a_3 + a_4 + a_5)/(a_3 + a_4) \times a_3]$. The percentage of unbound fraction or the free fraction was calculated by $[a_6/a_2 \times 100]$. Non-specific binding of [^{14}C]-SU5416 to the Centrifree tube before ultrafiltration and to the filtrate cup was within 0–8 and 7–27%, respectively, in all species tested.

Interspecies scaling analysis

The allometric relationship of the parameters of interest (Y) of SU5416 were correlated with the bodyweight (W) using an allometric equation: $Y = aW^b$, where a and b are the allometric coefficient and exponent, respectively. The values of a and b were estimated by least-squares fitting of log (Y) versus log (W) data, for each parameter. Statistical significance of the correlation was tested using the Student's *t*-test. A value of $P > 0.05$ was considered to be statistically significant.

The correlation between the parameters of interest and the bodyweight was performed across species including human data. For the prediction of the pharmacokinetic parameters in humans, the allometric relationship of the parameters of interest was estimated using animal data only. With the allometric equations obtained, the parameters of interest of SU5416 in humans were estimated and compared with the observed data in humans.

Results

Pharmacokinetics of SU5416

The plasma concentration–time profiles of SU5416 in different species are shown in Figure 2. The pharmacokinetic parameters of SU5416 studied in mouse, rat, dog and humans are presented in Table 1. SU5416 showed a biphasic exponential decline in plasma concentrations with a rapid distribution phase with a mean distribution half-life within 7 min in all species studied. Mean steady-state volume of distribution (Vd_{ss}) ranged from 0.98 to 1.9 L kg^{-1}, which is 1.5- to 3-fold greater than the body water volume (0.67 L kg^{-1}). The elimination of the unchanged SU5416 in urine was studied in rats and humans (data not shown), demonstrating that the renal pathway was a minor elimination route in both species. Less than 1% and an average 5.4% of administered dose were eliminated in 24 h after intravenous administration in rats (16.6 mg kg^{-1}) and in humans (145 mg m^{-2}), respectively. Therefore, the hepatic clearance (CL_H) of SU5416 can be estimated to approximate the systemic clearance. The blood to plasma ratio of SU5416 is near unity for rodents (data not shown), thus, the blood clearance can be estimated to be approximately equal to the plasma clearance. Clearance rates of SU5416 in all species studied were

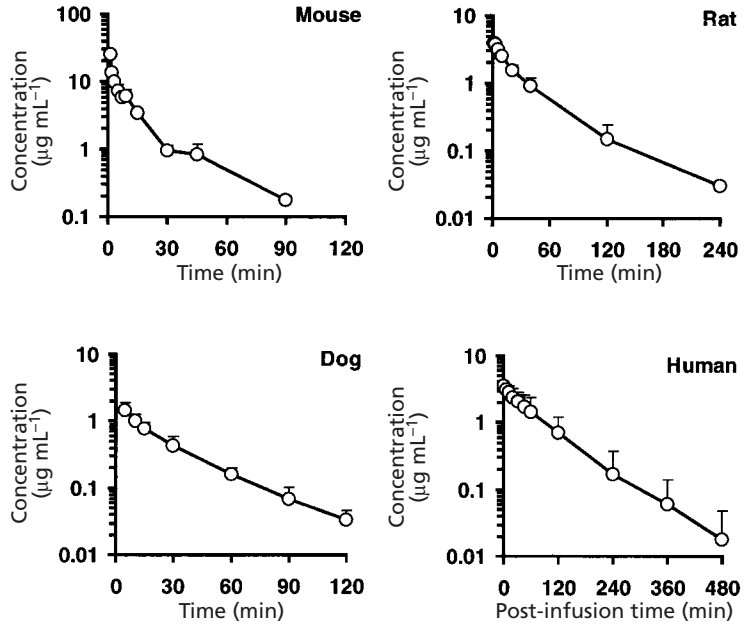


Figure 2 Plasma concentration–time profiles of SU5416 in different species.

Table 1 Pharmacokinetic parameters of SU5416 in mouse, rat, dog and humans.

Parameter	Mouse	Rat	Dog	Human[a]
n[b]	4[b]	4	6	69
Dose (mg kg^{-1})	16.7	5	2	0.1–5[c]
CL_s (mL min^{-1} kg^{-1})	96	45 ± 12	52 ± 14	14 ± 7
CL_R (mL min^{-1} kg^{-1})	–	0.001	–	–
Vd_{ss} (L kg^{-1})	1.9	1.6 ± 0.1	1.4 ± 0.4	0.98 ± 0.20
Distribution half-life (min)	4	6 ± 1	4 ± 2	7 ± 2
Elimination half-life (min)	24	31 ± 6	23 ± 3	50 ± 15
CL_{int} (mL min^{-1} kg^{-1})[d]	56	20	16	3[e]
% Plasma protein binding	97.8 ± 0.6	99.3 ± 0.1	–	99.2 ± 0.2

[a]Cancer patients with advanced malignancies on a variety of concomitant medications; [b]number of mice per time-point; [c]4.4–190 mg m^{-2}; [d]estimated from in-vitro metabolic stability studies using microsomal incubation, the value in monkey was 6 mL min^{-1} kg^{-1}; [e]using human liver microsomes (n = 15) from a bank of liver microsomes.

comparable with the corresponding liver blood flow, except for the dog, where the clearance rate was about 67% greater than the hepatic blood flow, suggesting possible extra hepatic elimination in this species. The elimination half-life ($t_{\frac{1}{2}}$) of SU5416 was short in animals, ranging from 24 to 31 min, but was longer in humans (50 min). The pharmacokinetics of SU5416 in humans was dose-independent over the range of 4.4–190 mg m^{-2}. Therefore, the parameters at all dose levels were averaged for interspecies comparison.

In-vitro metabolic profiling across species was extensively studied by Antonian et al (2000). All in-vitro metabolites observed in human liver microsomes were also formed by liver microsomes from mice, rats and dogs. In contrast, only some metabolites formed by monkey liver microsomes matched those found in humans. Similar in-vivo metabolites were also observed in the plasma of rodents, dogs and humans.

In-vitro metabolic stability in the liver microsome incubation of SU5416 showed that monkeys had the

greatest metabolic rate. The reported rates of metabolism by mouse, rat, dog, monkey and human liver microsomes were 652, 616, 218, 884 and 89 pmol min^{-1} $(mg\ protein)^{-1}$, respectively (Antonian et al 2000). The estimated CL_{int} (mL $min\ kg^{-1}$) of SU5416 was low in humans and higher in the smaller species (Table 1). The binding of SU5416 to plasma protein was high ($\geqslant 98\ \%$) and was concentration-independent over the concentration range of 0.06–8 $\mu g\ mL^{-1}$. Plasma protein binding of SU5416 was similar between the rats and humans.

Interspecies correlation of pharmacokinetic parameters and CL_{int} of SU5416

The plasma clearance (CL_s), Vd_{ss}, and CL_{int} of SU5416 showed good allometric relationship to bodyweight across the species studied (Figure 3). However, owing to a slight deviation from the regression line of CL_s and $t_{\frac{1}{2}}$ values for dog, and CL_{int} for monkey, the allometric analysis was then performed excluding those values. When the data from dog and monkey were excluded from the allometric analysis, the correlation of all parameters was improved. The $t_{\frac{1}{2}}$ parameter had a poor correlation with the body size (r^2 of 0.394 was observed for the correlation across species including humans). An improved r^2 of 0.998 was observed when the $t_{\frac{1}{2}}$ was correlated with the bodyweight of the rodents and humans. The allometric relationship of the parameters of interest is presented in Table 2.

Table 2 Allometric relationship of the pharmacokinetic parameters of SU5416 across species.

Parameter	Allometric equation (r^2; P value)	
	Mouse, rat, dog, human	Mouse, rat, human
CL_s (mL min^{-1})	$CL_s = 45W^{0.80}$ (0.979; $P < 0.05$)	$CL_s = 37W^{0.76}$ (0.999; $P < 0.05$)
CL_{int} (mL min^{-1})	$CL_{int} = 15W^{0.66}$ (0.976; $P < 0.01$)[a]	$CL_{int} = 13W^{0.64}$ (0.999; $P < 0.05$)
Vd_{ss} (L)	$Vd_{ss} = 1.5W^{0.92}$ (0.999; $P < 0.01$)	$Vd_{ss} = 1.4W^{0.92}$ (1.000; $P < 0.01$)
$t_{\frac{1}{2}}$ (min)	$t_{\frac{1}{2}} = 30W^{0.06}$ (0.394; $P = 0.37$)	$t_{\frac{1}{2}} = 34W^{0.09}$ (0.998; $P < 0.05$)

[a]Allometric analysis including mouse, rat, dog, monkey, and humans.

Prediction of the pharmacokinetic parameters of SU5416 in humans

The allometric relationships of CL_s, Vd_{ss}, CL_{int} and $t_{\frac{1}{2}}$ of SU5416 in the preclinical species and the prediction of these parameters in humans are demonstrated in Table 3. The same analysis was performed using rodent (mouse and rat) data to predict human pharmacokinetic parameters. The prediction of CL_s, CL_{int}, Vd_{ss}, and $t_{\frac{1}{2}}$ of SU5416 for humans is summarized in Table 3. Using the interspecies scaling, including mouse, rat and dog data,

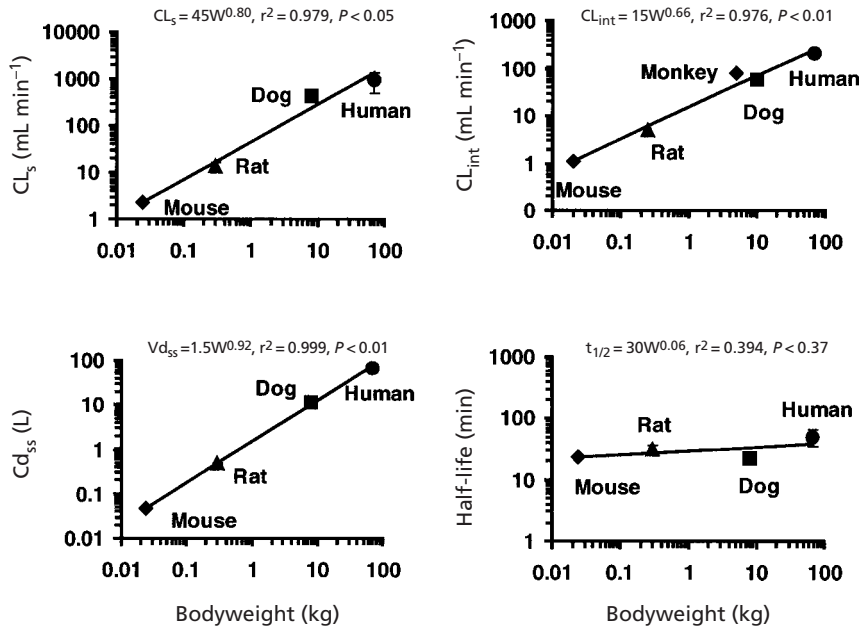


Figure 3 Interspecies correlation of pharmacokinetic parameters and CL_{int} of SU5416.

Table 3 Prediction of pharmacokinetic parameters of SU5416 in humans by extrapolating from the data from rodents and preclinical species.

Parameter	Species	Allometric equation (r^2)	Human data	
			Predicted	Observed
CL_s (mL min^{-1})	Mouse, rat, dog	$CL_s = 55W^{0.90}$ (0.989)	2564	
	Mouse, rat	$CL_s = 31W^{0.70}$	614	949 ± 461
CL_{int} (mL min^{-1})	Mouse, rat, dog, monkey	$CL_{int} = 16W^{0.70}$ (0.971)	322	
	Mouse, rat	$CL_{int} = 11W^{0.58}$	130	207
Vd_{ss} (L)	Mouse, rat, dog	$Vd_{ss} = 1.5W^{0.95}$ (1.000)	87	
	Mouse, rat	$Vd_{ss} = 1.5W^{0.93}$	77	69 ± 14
$t_{\frac{1}{2}}$ (min)	Mouse, rat, dog	$t_{\frac{1}{2}} = 25W^{-0.01}$ (0.043)	24	
	Mouse, rat	$t_{\frac{1}{2}} = 35W^{0.10}$	54	50 ± 15

the prediction of CL_s, CL_{int}, and $t_{\frac{1}{2}}$ for humans was 2.7-fold greater, 1.6-fold greater, and 3.6-fold lower than the observed values, respectively. An excellent prediction was obtained using the extrapolation from rodent data, where the prediction of CL_s and CL_{int} for humans was 1.6-fold lower than the observed values and that of $t_{\frac{1}{2}}$ was within the observed range in cancer patients. The Vd_{ss} was accurately predicted, within the observed range, using both approaches of including and excluding the dog data.

Discussion

The pharmacokinetics of SU5416, a novel VEGF receptor inhibitor, were examined in preclinical species as part of its preclinical development. SU5416 can be classified as a high-clearance compound. The renal excretion of the compound was small, indicating that the primary route of elimination is through the liver. This finding was consistent with the excretory data of the total radioactivity of administered [^{14}C]SU5416 in rats showing that 72 % of the dose was eliminated in the faeces through biliary excretion and only 16 % of the dose was recovered in the urine after intravenous administration (data not shown).

Although the plasma protein binding of SU5416 was high, owing to a lack of plasma protein binding data in the dog, the pharmacokinetic parameters of SU5416 were estimated using the total plasma concentration without correction for the extent of plasma protein binding and were used for the interspecies scaling.

The primary aim of performing interspecies scaling of SU5416 was to test whether there was a correlation of the key pharmacokinetic parameters between animals and humans. The analysis showed that the Vd_{ss} correlated well with the bodyweight and it appears to be directly proportional to bodyweight with the exponent b of 0.92 (Table 2). The correlation of SU5416 CL_s and CL_{int} to bodyweight was also good, with the exponent b of 0.80 and 0.66, respectively, which was close to 0.75, the reported value for the metabolic rate (Weiss et al 1977; Mordenti & Chappell 1989; Tse 1995). Since the clearance value of SU5416 was high and approximates the hepatic blood flow, the scaling of the clearance of the compound is a reflection of the scaling of the hepatic blood flow, a physiological parameter. As mentioned above, the CL_s in the dog was different from other species, being exceptionally greater than hepatic blood flow, and the in-vitro metabolic rate in the monkey was remarkably high compared with other species. This may explain the deviation from the regression line of CL_s for dog and CL_{int} for monkey. When the dog and monkey were excluded from the allometric analysis, the correlation of all parameters, including Vd_{ss}, was improved. The correlation for the $t_{\frac{1}{2}}$ of SU5416 was poor and independent of bodyweight.

Using the interspecies scaling including mouse, rat, dog and monkey (for CL_{int}) data, the prediction of CL_s, CL_{int}, and $t_{\frac{1}{2}}$ for humans was reasonably good, within 4-fold of the observed values. As expected, a superior prediction (within 2-fold of the observed values) was obtained using the extrapolation from rodent data only, suggesting that the rodent data are sufficient for the scale-up of SU5416 pharmacokinetic parameters in humans. The Vd_{ss} was predicted accurately by both approaches (with and without dog data).

In summary, SU5416 had similar disposition kinetics in all species tested, except for the dog, where a higher clearance rate was observed. CL_s, CL_{int}, and Vd_{ss} correlated well with bodyweight ($r^2 > 0.97$). It was possible to

use the allometric equation to make reasonable predictions of the pharmacokinetic parameters of SU5416 in cancer patients with various types of solid tumours. Pharmacokinetic data from rodents are apparently more predictive of human pharmacokinetics than data from non-rodents.

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