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Pharmacokinetics of the 8-methoxyquinolone, moxifloxacin: a comparison in humans and other mammalian species

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The pharmacokinetics of moxifloxacin was investigated in NMRI mice, Wistar rats, rhesus monkeys, beagle dogs, Göttingen minipigs and healthy human volunteers after iv and oral administration of moxifloxacin-HCl (single doses of moxifloxacin 9.2 mg/kg bodyweight) in animals and 100 mg moxifloxacin (1.4 mg/kg bodyweight po and 1.2 mg/kg bodyweight iv) in humans. The plasma concentration *vs* time courses of the unchanged compound (determined by HPLC) and the derived pharmacokinetic parameters were used to evaluate the absorption process, to compare the pharmacokinetics in these species and to perform an interspecies scaling. The results of the pharmacokinetic investigations indicate a clear dependence on the species. Moxifloxacin is absorbed quickly (rats, dogs, humans > monkeys): the major portion of the dose reached the systemic circulation within the first 2 h. In the minipig absorption was slower. Bioavailability was high to moderate (91–52%) in all species. Protein binding (f_u) was low (55–71%) in all species. The volume of distribution at steady state (V_{ss}) was medium to large (2.0–4.9 L/kg) in all species. There were considerable differences in maximum concentrations ($C_{max,norm}$, 0.430–0.070 kg/L) and in AUC_{norm} values (oral, 6.18–0.184 kg·h/L; iv, 7.51–0.237 kg·h/L). Total body clearance (*CL*) decreased with increasing bodyweight (4.21–0.132 L/(h·kg)). The mean residence time (MRT) decreased with decreasing bodyweight (15–0.88 h). The half-life ($t_{½}$) decreased with decreasing bodyweight (oral, 12–1.3 h, iv, 13–0.93 h). There was moderate to low renal excretion (iv, 20–6.2%), the renal clearance, (CL_R) was in the range 0.615–0.0222 L/(h·kg). Regarding the pharmacokinetic parameters determined after oral administration, the dog was most similar to the human in terms of C_{max}, AUC and $t_{½}$. There was good correlation between bodyweight and *CL* (coefficient of correlation (r) = 0.959), V_{ss} (r = 0.990) and MRT (r = 0.943). On the basis of preclinical studies a terminal half-life appropriate for once-daily dosing in humans was predicted and confirmed by Phase I data.

Introduction

Moxifloxacin is a new 8-methoxyquinolone with a broad spectrum of antibacterial activity against Gram-positive and Gram-negative bacteria, anaerobes and atypical organisms such as *Mycoplasma*, *Legionella* and *Chlamydia* spp. The antibacterial activity is independent of β-lactamase production or altered β-lactam target sites and macrolide resistance. The pronounced and rapid bactericidal activity against Gram-positive bacteria is concentration-dependent.[1] Moxifloxacin exerts a marked post-antibiotic effect against clinically relevant microorganisms.[2] Moxifloxacin effectively penetrates extravascular tissue[3] and is currently under clinical development for the treatment of infections caused by susceptible microorganisms.

BAY 12-8039, representing moxifloxacin-HCl, was administered to mice, rats, monkeys, dogs, minipigs and healthy human volunteers in single oral and iv doses to investigate the rate of absorption, to evaluate the absorption process and to compare the pharmacokinetics of moxifloxacin in these mammalian species and to perform an interspecies scaling. In-vitro investigations on protein binding and erythrocyte/plasma partitioning were also performed.

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Materials and methods

Chemicals, reagents and biological material

Moxifloxacin (1-cyclopropyl-7-[(*S*,*S*)-2,8-diazabicyclo-[4.3.0]non-8-yl]-6-fluoro-8-methoxy-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid) was synthesized at Bayer AG, Leverkusen and Wuppertal, Germany.[4] For in-vitro investigations radiolabelled compound was also used. ^{14}C-Labelled BAY 12-8039 labelled at position 3 of the quinolone was synthesized by M. Conrad at Bayer AG, Wuppertal, Germany. Two batches, with a specific radioactivity (related to moxifloxacin) of 3.23 and 3.04 MBq/mg and a radiochemical purity of 99% were used.

Animals

The animals used were: male NMRI mice (weighing 26–43 g; aged approximately 6 weeks; Harlan-Winkelmann, Borchen, Germany; $n = 3$ per time point); male Wistar rats (weighing 175–225 g, aged 6–7 weeks; Harlan-Winkelmann; $n = 3$ per time point); female rhesus monkeys (weighing 3.5–5.2 kg; aged 4–7 years; Hazleton, Münster, Germany, $n = 3$; female beagle dogs (weighing 8.7–15.6 kg; aged 3–6 years, Marshall Farms USA, Inc., North Rose, NY, USA, $n = 3$; and female Göttingen minipigs (weighing 10.9–17.6 kg; aged 1–2 years; Ellegaard, Dalmose, Denmark; $n = 3$).

Before dosing the animals had been adapted to the laboratory conditions for at least 1 week at 20–24°C and 45–65% humidity. The animals were fed with appropriate diets (mice, rats: Altromin 1324, Altromin GmbH, Lage, Germany; monkeys: Altromin 6024 (Altromin GmbH); minipigs: Altromin 9023 (Altromin GmbH), dogs: Ssniff Hd-Haltung (Ssniff Spezialdiäten GmbH, Soest, Germany) plus Ovator Hundemenu Vital (Muskator Werke, Barnewitz/Moll GmbH, Düsseldorf, Germany). The monkeys were additionally fed with fruit. For the rats a restricted feeding procedure was used for at least 1 week before dosing: 15 g food was given per day at noon. This ensured fasting overnight for 14–16 h before administration of the test compound. The other animals used were also fasted overnight before the administration of the test compound.

Human volunteers

Phase I studies[5,6] were performed on healthy male Caucasian volunteers, under standardized conditions according to the principles of the Declaration of Helsinki and approved by the local ethics committee.

Dosage form, doses and routes of administration

BAY 12-8039 represents moxifloxacin as the hydrochloride salt and in the studies described concentrations of unchanged compound were determined and expressed as moxifloxacin equivalents. For the preclinical investigations moxifloxacin-HCl was dissolved in physiological saline, the concentrations ranging from 0.92 to 9.2 mg/mL moxifloxacin (corresponding to 1–10 mg/mL BAY 12-8039). All formulations used for animal experiments were prepared immediately before administration. Stability of the test compound in the formulation used for iv and po administration to animals was verified for at least 2 h by HPLC. For the Phase I studies a 50 mg moxifloxacin tablet formulation (po) and a 0.2% aqueous solution (iv) were used.[5–7] The formulations of the test compound were given as single iv administrations via a caudal vein (mice, rats), a cubital vein (humans), a cephalic or saphenous vein (dogs, monkeys) or an ear vein (minipigs). The iv doses were given either as a bolus injection (mice, rats) or as a short infusion (dogs, monkeys, minipigs (over 15 min) humans (over 30 min)) via a calibrated syringe attached to a suitable infusion pump. Oral doses were given either by gavage or via a stomach tube (experimental animals) or as tablets (humans). The doses administered amounted to 9.2 mg or 2.8 mg moxifloxacin (corresponding to 10 or 3.0 mg/kg bodyweight BAY 12-8039 as single doses in experimental animals and 100 mg moxifloxacin po and iv (corresponding to approximately 1.4 mg/kg bodyweight moxifloxacin po and 1.2 mg/kg bodyweight iv, respectively) in humans under fasted conditions. The dogs, monkeys and minipigs were dosed iv as well as orally to enable intra-individual comparison to be made, using a suitable washout period of 1–2 weeks.

Specimen collection and processing

Collection of samples. Blood samples were collected by exsanguination from a carotid artery in anaesthetized rats or from a retroorbital venous plexus in anaesthetized mice or from a punctured jugular, saphenous, cephalic, brachiocephalic vein, or a carotid artery in conscious dogs, monkeys and minipigs. In humans a cubital vein was preferred for blood sampling.[6] Blood was collected into heparinized syringes. Plasma was obtained by centrifugation of blood samples. The plasma was stored below −15°C before further analysis.

Determination of unchanged moxifloxacin in plasma. The following method was used for the analytical determination of moxifloxacin concentrations in the plasma of monkey, dog, minipig, rabbit, rat and mouse. The moxifloxacin concentrations in plasma were determined by HPLC and fluorescence detection. After addition of 10 μL of an internal standard to 0.2 mL plasma, 0.2 mL acetonitrile was added. Plasma proteins were precipitated by shaking in an ultrasonic bath followed by centrifugation for 10 min at 1550**g**. The supernatant was diluted 4-fold with 0.067 molar disodium hydrogen phosphate buffer pH 7.5 and trans-

ferred to HPLC autosampler vials. The calibration curve was prepared by spiking blank plasma with seven different concentrations between 5 and 1000 μg/L. Independently of the calibration samples, quality control samples with three different concentrations were prepared in the respective blank matrix and analysed together with the unknown samples for validation purposes. The HPLC separation was performed using a Hewlett Packard 1090A high-performance liquid chromatograph with HP ChemStation software (Hewlett Packard Co., Düsseldorf, Germany) and a Jasco Model FP 920 S fluorescence detector (Jasco, Labor- und Datentechnik GmbH, Gross-Umstadt, Germany). The chromatography was done at 5°C on a reversed-phase Nucleosil C_{18} column, 250 × 4 mm, 5 μm particle size (Muder and Wochele, GmbH, Berlin, Germany) with an injection volume of 50 μL. The mobile phase consisted of acetonitrile and tetrabutylammonium hydrogensulphate solution in Milli-Q Plus water, 10 g/L (Millipore GmbH Eschborn, Germany). A gradient from 20% (1 min) to 41% acetonitrile (within 9 min) with a flow rate of 1.0 mL/min was used. Moxifloxacin and the internal standard eluted at approximately 7.3 and 8.1 min, respectively. The fluorescence detection was performed at an excitation wavelength of 296 nm and an emission wavelength of 504 nm.

For the construction of the calibration curves the relative peak height was used with $1/y^2$ weighted regression (CONCALC 1.23, software package, Bayer AG). The lower limit of quantification for plasma was 5.0 μg/L. The inter-assay precision (relative standard deviation) ranged from 1.2% to 8.1% (rat plasma) and from 3.9% to 6.8% (monkey plasma). The inter-assay accuracy (relative deviation from the nominal value, calculated from the quality control samples) ranged from −11% to −3.6% (rat plasma) and from 4.0% to 7.3% (monkey plasma), respectively.

The analytical determination of moxifloxacin concentrations in human plasma was performed by HPLC with fluorescence detection according to Stass & Dalhoff.[8] Precision ranged between 3.1% and 5.2% and accuracy between 4.6% and 5.8%, respectively, throughout the whole working range of the method.

Determination of the [^{14}C]BAY 12-8039-associated radioactivity in plasma and urine. The radioactivity concentrations in plasma and urine samples were measured without further processing using liquid scintillation counting.

Binding to plasma proteins. The binding of ^{14}C-labelled BAY 12-8039 to plasma proteins in mice, rats, monkeys, dogs, minipigs and humans was determined *in vitro* using an ultrafiltration device with membranes of narrow pore size (Centri free micropartition system with YMT ultrafiltration membranes; Amicon GmbH, Witten, Germany). [^{14}C] BAY 12-8039 was added to about 1 mL of plasma at defined concentrations and centrifuged at 1800**g** for 10 min. The free (unbound) fraction (f_u) was calculated according to the formula

$$f_u = \frac{C_u}{C} \times 100[\%].$$

Where C_u is the concentration unbound and C is the total concentration.

Erythrocyte/plasma partitioning. To determine the partitioning to erythrocytes/blood cells *in vitro*, the test substance was dissolved in a small volume of a suitable solvent and then added to carbogen-equilibrated whole blood or erythrocyte suspensions and incubated until reaching equilibrium on a laboratory shaker. Blood cells were separated from the aqueous phase by centrifugation after taking aliquots for determining the radioactivity in the whole blood. The erythrocyte/plasma partition coefficient ($P_{E/P}$) is defined as:

$$P_{E/P} = \frac{C_E}{C_P}$$

$$C_E = \frac{C_B - C_P(1 - HC)}{HC}$$

Where C_B is the concentration in whole blood, C_P the concentration in plasma, HC the haematocrit, and C_E the concentration in erythrocytes.

Data evaluation. Pharmacokinetic evaluation of the concentration–time data was performed by non-compartmental analysis[9–10] using the KINCALC software package, Bayer AG (version 2.33 or higher). The areas under the concentration–time curves were calculated using the mixed linear-logarithmic trapezoidal rule,[11] followed by extrapolation of the AUC to infinity by dividing the calculated concentration at the last observation time point from the slope of the regression line by the terminal elimination rate constant.[11] Pharmacokinetic symbols used are in accordance with the ACCP nomenclature recommendations.[12] Pharmacokinetic parameters and concentration values are given as geometric means and S.D. (1s range: $\bar{x}_g/s_g$; $\bar{x}_g \cdot s_g$), while protein binding data and renal excretion are given as arithmetic means with S.D.

The cumulative absorption of moxifloxacin (absorption process) was calculated by a deconvolution technique.[13] In rats and humans geometric mean plasma concentration–time profiles from iv reference studies were used for an inter-individual comparison, whereas in monkeys, dogs and minipigs intra-individual comparison could be performed.

The allometric scaling (correlation with bodyweight) of the pharmacokinetic parameters—volume of distribution at steady state (V_{SS}), total body clearance (CL) and mean residence time (MRT)—was performed according to

Boxenbaum[14] and Adolph[15] using different doses (rats, monkeys, humans). After logarithmic/logarithmic transformation the individual species parameters were fitted to equation $y = a \cdot BW^b$ where y is a variable describing a pharmacokinetic parameter, BW is the bodyweight and a and b represent the allometric coefficient and the allometric exponent, respectively.

Absolute bioavailability in the different species was estimated based on inter-individual exposure data (AUC_{norm}) except for dogs, minipigs and monkeys, where intra-individual comparison was possible.

Results

Binding to plasma proteins and erythrocyte/plasma partitioning

The binding of [^{14}C]BAY 12-8039 to plasma proteins of male mice and rats, female monkeys, dogs and minipigs and male humans is low. Determinations were performed for three concentrations between 0.1 and 10 μg/L. The free fractions (means) were 55–71% (human < monkey, rat, minipig < mouse < dog) (Table I). No concentration-

Table I. Pharmacokinetic parameters (geometric mean (S.D.)) of moxifloxacin calculated from the concentration–time courses of the unchanged compound in the plasma and the amounts excreted via urine after single administration of BAY 12-8039.

	Species					
Parameter	mouse (male)	rat (male)	monkey (female)	dog (female)	minipig (female)	human (male)
Dose (mg/kg)[a]						
po	9.2	9.2	9.2	9.2	9.2	*c*. 1.4
iv	9.2	9.2	2.8	2.8	2.8	*c*. 1.2
Mean bodyweight (kg)	0.029	0.19	4.5	12	14	73 (po), 85 (iv)
CL (L/(h·kg))	4.21	2.55	0.692 (1.39)	0.222 (1.33)	0.645 (1.39)	0.132 (1.11)
V_{SS} (L/kg)	3.7	3.6	4.9 (1.32)	2.7 (1.28)	3.8 (1.20)	2.0 (1.08)
f_u (%)	69	63	62	71	63	55
$P_{E/P}$ (%)	ND	1.25	1.13	ND	ND	1.09
MRT_{tot} (h)						
po	2.0	1.5	9.4 (1.24)	14 (1.25)	14 (1.10)	18 (1.13)
iv	0.88	1.4	7.2 (1.05)	13 (1.16)	6.0 (1.16)	15 (1.07) [b]
$t_{½}$ (h)						
po	1.3	1.3	7.2 (1.15)	9.0 (1.13)	11 (1.10)	12 (1.11)
iv	0.93	1.2	6.9 (1.07)	8.6 (1.18)	5.7 (1.01)	13 (1.10)
f (%)	78	78	52 (1.21)	91 (1.13)	*c*. 54	82[c]
$C_{max,norm}$ (kg/L)						
po	0.137	0.312	0.0864 (1.75)	0.251 (1.33)	0.0704 (1.17)	0.430 (1.23)
t_{max} (h)	0.25	0.0833	4.0 (2.0)	1.6 (2.88)	4.0 (1.0)	2.0 (1.90)
AUC_{norm} (kg·h/L)						
po	0.184	0.305	0.757 (1.40)	4.09 (1.18)	0.840 (1.41)	6.18 (1.18)
iv	0.237	0.392	1.44 (1.39)	4.51 (1.33)	1.55 (1.39)	7.51 (1.09)
Ae_{ur}[d] (%)						
po	14	7.8	4.5	ND	ND	19
iv	14	8.4	6.2	8.5	13	20
CL_R (L/(h·kg))						
iv	0.615	0.216	0.0421 (1.21)	0.0222	0.0893	0.0261 (1.28)
GFR·f_u[e] (L/(h·kg))	0.414	0.328	0.0744	0.170	ND	0.0594

ND, Not determined.
[a] Normalized to moxifloxacin.
[b] MRT_{iv}
[c] Interindividual comparison.
[d] Arithmetic means.
[e] GFR data obtained from literature.[23,24]

dependence was seen. Following precipitation of plasma proteins by ethanol and six subsequent washings with ethanol, the reversibility of the protein binding in rat and human plasma was demonstrated.

The affinity of [^{14}C]BAY 12-8039 for erythrocytes in moderate. The erythrocyte *vs* plasma partition coefficients were 1.25 (male rats), 1.13 (female monkeys) and 1.09 (male humans) (Table I).

Plasma concentrations after intravenous administration

The dose-normalized plasma concentration–time courses moxifloxacin following iv administration of 9.2 or 2.8 mg/kg of bodyweight to mice, rats, monkeys, dogs and minipigs are shown in Figure 1 and are compared with the plasma curve of humans (iv infusion of *c*. 1.2 mg/kg bodyweight). The derived AUC_{norm} in the animals ranged from 4.51 to 0.237 kg·h/L (dog >> minipig, monkey > rat > mouse). For humans a higher value (7.51 kg·h/L) was determined.

Total plasma clearance (CL) in the animals ranged from 0.222 to 4.21 L/(h·kg) (mouse > rat >> monkey, minipig > dog), with all values being higher than that determined for humans (*c*. 0.132 L/(h·kg)). The renal clearance (CL_R) ranged from 0.0222 to 0.615 L/(h·kg) (rat > minipig > monkey, dog, mouse). CL_R for humans was 0.0261 L/(h·kg). The V_{SS} ranged from 4.9 to 2.7 L/kg (monkey > rat, minipig, mouse > dog). For humans a lower V_{SS} of 2.0 L/kg was determined. For the elimination from plasma after iv administration the MRTs were between 12 and 0.88 h (dog > monkey, minipig > rat, mouse), and half-lives ($t_{½}$) ranged from 8.6 to 0.93 h (dog > monkey > minipig >> rat, mouse). In humans the MRT and $t_{½}$ were longer (15 h and 13 h, respectively). Further parameters are listed in Table I.

Plasma concentrations after oral administration

In animals the dose-normalized maximum concentration of moxifloxacin in the plasma ($C_{max,norm}$) ranged from 0.312 to 0.0704 kg/L (rat > dog > mouse > monkey, minipig). For humans a higher $C_{max,norm}$ (0.430 kg/L) was determined. AUC_{norm} ranged from 4.09 to 0.184 kg·h/L in animals and was 6.18 kg·h/L in humans. Oral bioavailability was between 91% and 52% (dog > rat, mouse > minipig, monkey). In humans a bioavailability of 82% was estimated by inter-individual comparison (Table I). Further parameters are listed in Table I. The concentration–time courses of moxifloxacin are compared in Figure 2.

Absorption process

Moxifloxacin was absorbed rapidly (rat, dog, human > monkey): the major portion of the dose reached the systemic circulation within the first 2 h. Fifty percent of the oral bioavailability ($f_{50\%}$) was achieved between 5 min and 2 h. In the minipig, absorption was slower ($f_{50\%}$ = 4 h), (Figure 3).

Interspecies scaling

Using allometric scaling,[14,15] a good correlation could be shown between humans and animals for CL (coefficient of correlation (r) = 0.959), V_{SS} (r = 0.990) and MRT (r = 0.943), (Figure 4).

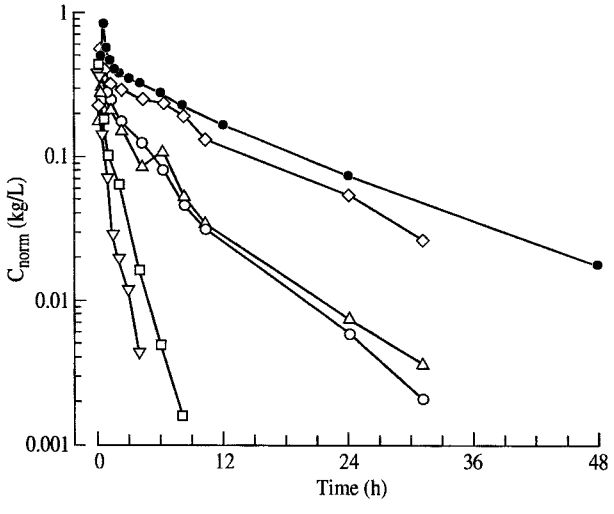

Figure 1. Mean dose-normalized plasma concentration–time courses of moxifloxacin in different mammalian species after a single iv administration of 1.2 mg/kg bodyweight moxifloxacin (human; infusion over 30 min, ●), 9.2 mg/kg bodyweight moxifloxacin (mouse (▽), rat (□); bolus injection) or 2.8 mg/kg bodyweight moxifloxacin (monkey (△), dog (◇), minipig (○); infusion over 15 min).

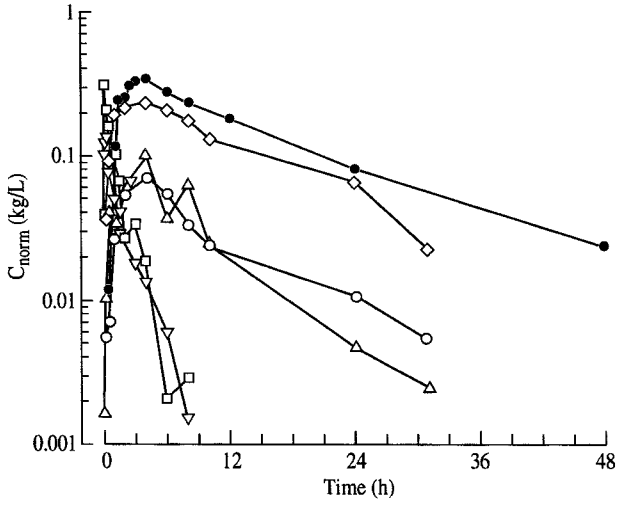

Figure 2. Mean dose-normalized plasma concentration–time courses of moxifloxacin in different mammalian species after a single oral administration of moxifloxacin 1.4 mg/kg bodyweight moxifloxacin (human (●)) and 9.2 mg/kg bodyweight moxifloxacin (◇, dog; △, monkey; ○, minipig; □, rat; ▽, mouse).

Discussion

This paper reports on investigations with the new quinolone moxifloxacin and focuses on the rate of absorption, the protein binding *in vitro*, the erythrocyte/plasma partitioning, the dependence of the pharmacokinetics of moxifloxacin on the species and the allometric scaling of selected pharmacokinetic parameters. [^{14}C]BAY 12-8039 had low plasma protein binding with very slight species differences. The smallest unbound fraction was in human plasma (55%) and the highest (71%) in dog plasma, probably due to the lower albumin concentration in dog plasma. The drug was mainly bound to albumin, and the binding was fully reversible. A low protein binding generally enables a rapid and extensive distribution into the intra- and extracellular space. The erythrocyte *vs* plasma partition coefficients as measured *in vitro* were similar in rat, monkey and humans (range 1.25–1.09), thus indicating a moderate affinity of [^{14}C]BAY 12-8039 to erythrocytes. Accordingly, the blood concentrations were up to 1.14 times higher than the corresponding plasma concentrations.

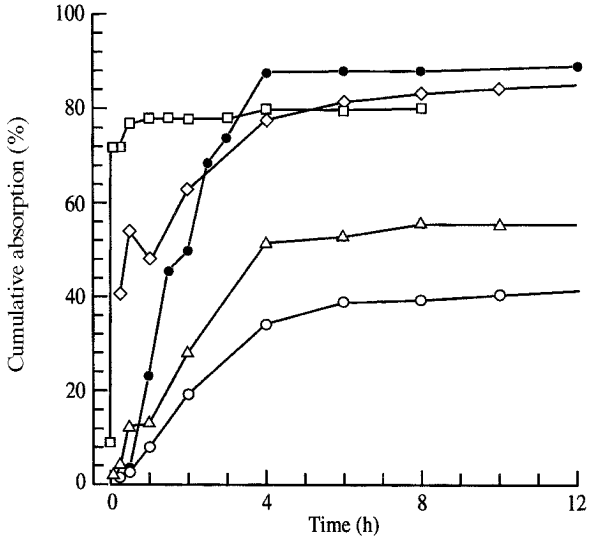

Figure 3. Cumulative absorption of moxifloxacin in different species calculated by a deconvolution technique[8] using the plasma concentration–time courses of the unchanged compound after single iv and oral administration of BAY 12-8039 (●, human; ◇, dog; □, rat; △, monkey; ○, minipig)

As described previously[16] [^{14}C]BAY 12-8039 is absorbed almost completely in rats and rhesus monkeys. In the present study, high bioavailabilities were found in mouse, rat, dog and humans, indicating an almost complete absorption in these species. From deconvolution data, rapid absorption of the unchanged compound (rats, dogs, human > monkey) was derived. In these species the major portion of the systemically available dose was absorbed within 2 h. A distinctly slower absorption occurred in the minipig resulting in a higher $f_{50\%}$ of 4 h. This might be due to anatomical as well as physiological characteristics of the pig stomach, especially in fasted animals, as discussed elsewhere.[17–20]

V_{SS} was large to medium (4.9–2.0 L/kg) in all species. The high affinity for organs and tissues indicated by these values was confirmed in rats as described elsewhere.[16]

In the present investigations a clear correlation was found between bodyweight of the individuals and the pharmacokinetic parameters, CL, and V_{SS}. No correlation could be found between bodyweight, C_{max} or AUC_{norm} values after oral administration.

The total body clearance decreased with increasing bodyweight. Renal excretion was moderate to low (20–6.2% after iv administration), renal clearance ranging from 0.0222 to 0.615 L/(h·kg). This parameter was compared with the value GFR·f_u (representing the expected renal clearance if there was no reabsorption or active secretion). In rat, monkey, dog and human (no data were available for the minipig) GFR·f_u is higher than the observed renal clearance (Table I), indicating a partial tubular reabsorption of moxifloxacin. Half-life (1.3–12 h after po administration) and MRT (1.5–18 h) decreased with decreasing bodyweight. Due to the relatively long $t_{½}$ shown in larger animals, moxifloxacin should be appropriate for once-daily dosing. This was confirmed by Phase I studies[5–7] (and Stass, H. and Kubitza, D., personal communication).

The pharmacokinetic parameters determined in the dog

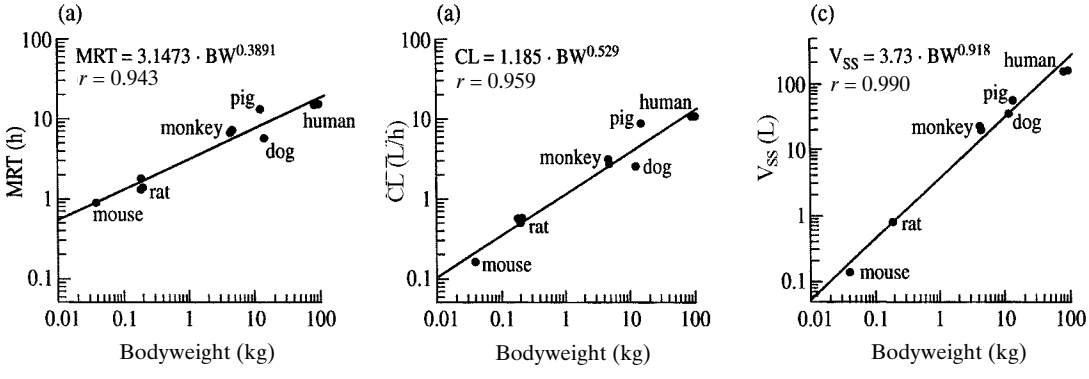

Figure 4. Allometric scaling[14,15] of the pharmacokinetic parameters (a) mean residence time (MRT); (b) total body clearance (CL); and (c) distribution at steady state (V_{SS}) of moxifloxacin in six different mammalian species. r, coefficient of correlation

were most similar to those in humans: $C_{max,norm}$ = 0.25 and 0.43 kg/L, AUC_{norm} = 4.09 and 6.18 kg·h/L, $t_{½}$ = 9.0 and 12 h in dogs and humans, respectively. A good correlation between the pharmacokinetic parameters determined for dogs and humans was also shown by Umemura *et al*.[21] for other fluoroquinolones.

Allometric scaling based on bodyweight[14,15] was successfully applied to the test compound using the concentration–time courses of moxifloxacin for mouse, rat, monkey, dog, minipig and humans and the derived pharmacokinetic parameters CL, V_{SS} and MRT (r = 0.959, 0.990 and 0.943, respectively). For other fluoroquinolones, a good correlation between humans and experimental animals (mice, rats, rabbits, dogs and monkeys) has also been demonstrated for apparent plasma clearance, renal clearance, and apparent steady state volume of distribution.[21,22]

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