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Interspecies Scaling of Roxithromycin Pharmacokinetics Across Species

Jong-Hwan Lim*, Byung-Kwon Park and Hyo-In Yun[1]**

**B&C Biopharm, Yongin-Si, Gyonggi-Do*
***JEONJINBIO, Hosan-Dong, Dalseo-Gu, Daegu*
College of Veterinary Medicine, Chungnam National University, Daejeon

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Abstract : The purpose of this study was to examine the allometric analysis of roxithromycin using pharmacokinetic data. The pharmacokinetic parameters used were half-life ($t_{1/2}$), mean residence time (MRT), clearance (Cl) and volume of distribution at steady state (V_{ss}). Relationships between body weight and the pharmacokinetic parameter were based on the empirical formula $Y = aW^b$, where 'Y' is $t_{1/2}$, MRT, Cl, or V_{ss}, W the body weight and 'a' is an allometric coefficient (intercept) that is constant for a given drug. The exponential term, 'b', is a proportionality constant that describes the relationship between the pharmacokinetic parameter of interest and body weight. As results of the allometric analyses, the logarithms of $t_{1/2}$, MRT, Cl, and V_{ss} were linearly related to the logarithms of body weight. Results of the current analyses could provide information on appropriate doses of roxithromycin for all species.

Key words **:** Roxithromycin, allometric analysis, interspecies, pharmacokinetics

Introduction

Drug dosage extrapolation among species assumes that pharmacodynamic similarities exist when pharmacokinetic equivalency is achieved (2,3,5,8,19). The allometric approach is a basic mathematical tool for analyzing differences in anatomy, physiology, biochemistry, and pharmacokinetics in animals of different sizes (2,8). At least 750 allometric equations have been reported (5). The usual allometric approach relates one biologic function or structure (y) to another (x) through an empirical power function (8).

Drug plasma concentrations are dependent on the pharmacokinetic parameters of the drug, including half-life, clearance, volume of distribution, or the area under the drug concentration vs. time curve. Because most pharmacokinetic parameters are dependent on physiologic functions, it is possible to compare these parameters among species on the basis of allometric relationships, i.e. where y is the value of the pharmacokinetic parameter and x the body weight. Allometry may be performed on any pharmacokinetic parameter, however, the half-life profile is most often studied because of the abundance of this parameter in the published literature (2,19).

Roxithromycin, chemically designated as (E)-erythromycin-9-[O-[(2-methoxyethoxy) methyl] oxime], is a semisynthetic, orally administered antibacterial macrolide structurally related to erythromycin. It has activity against some Staphylococcus spp., many Streptococcus spp., Moraxella catarrhalis, Mycoplasma pneumoniae, Legionella pneumophila and Chlamydia trachomatis as well as many less common organisms (4,14). In comparison with that of erythromycin, its parent compound, the pharmacokinetic profile of roxithromycin is characterized by high plasma, tissue and body fluid concentrations and a long half-life permitting an extended dosage interval (10,14,15). Erythromycin has been a popular antibiotic in human and veterinary medicine for the treatment of gram-positive infections (16,18). Although allometry can be an important tool for dose extrapolation of drugs, there was not any established allometric model of roxithromycin based on body weight in order to predict half-life ($t_{1/2}$), mean residence time (MRT), total body clearance (Cl) and volume of distribution at steady state (V_{ss}). Allometric model of roxithromycin should be required to more accurately extrapolate across species for the purpose of defining the effective dose of roxithromycin to be used in clinical settings.

Materials and methods

Animals

The animals used in the study were: Five male Sprague-Dawley rats (weighing 175-225 g; aged 6-7 weeks) six male New Zealand White rabbits (weighing 1,750-1,950 g). Rabbits were individually housed in stainless steel cages with grate floors. The animals were acclimatized for 1 week before the experiment. All animals had ad libitum access to water and were fed a commercial diet once daily. All animals had no previous exposure to any antibiotic and no drugs were given to the animals during the acclimation or study periods.

Experimental designs

For comparative pharmacokinetic study of roxithromycin

[1]Corresponding author.
E-mail : hiyun@cnu.ac.kr

was dissolved in the combination solution of dimethylsulfoxide (DMSO) and propylene glycol (PG), the concentrations 2-10 mg/mL. Roxithromycin was kindly supplied by Shinil Biogen (Anyang, Korea). This formulation used for animal experiments were immediately made before administration. Stability of the test compound in the formulation used for intravenous (i.v.) administration to animals was verified for at least 2 h by LC/MS. The formulations of roxithromycin were given as single i.v. administrations via a caudal vein (rats) and cephalic vein (rabbits). The intravenous doses were given to all animals as a bolus injection. The doses administered amounted to 20 mg roxithromycin/kg bodyweight (b.w.) in all animals.

Blood samples were taken from a punctured caudal vein (rats) and cephalic vein through preplaced 24 gauge 3/4 inch intravascular catheters (rabbits) at 0 (pre-), 0.25, 0.5, 1, 2, 4, 8, 12, 36 and 48 h following treatments. The blood samples were collected in heparinized vacutainers, promptly centrifuged and plasma samples were stored at -70°C until analysis.

Analytical methods

Roxithromycin were extracted from the plasma as previous reported by our laboratory and assayed by high performance liquid chromatography/mass spectrometry (11). The limit of quantitation of roxithromycin was 1 ng/mL, the inter-day and intra-day precision (CV, %) was 15% and calibrations were linear ($r > 0.999$) from 1 to 10000 ng/mL.

Pharmacokinetic analysis

Monoexponential and biexponential equations were fitted to individual plasma concentration-time data. Several models were investigated and the most appropriate one was chosen based on the coefficient of determination (r^2) and visual inspection of profiles. The plasma roxithromycin concentration vs. time profiles after i.v. administration and oral administration of roxithromycin were then analyzed by iterative nonlinear least squares regression analysis with equal weighting of the data using a WINNOLIN compartmental model program (Pharsight Corporation, California, USA). The estimation was performed with the use of the weighting model ($1/C^2$ predicted) for the estimation of pharmacokinetic parameters. Minimum Akaike Information Criterion Estimates (MAICE) was applied to discriminate the best fitting model.

Compartmental modeling was attempted for the i.v. data, and the best model chosen using the Akaike's Information Criterion and visual inspection of the weighted residual plots. The elimination half-life ($t_{1/2\beta}$) was calculated by $t_{1/2\beta} = 0.693/\beta$. The area under the plasma concentration vs. time curves for both the i.v. ($AUCi.v._{0-}$) and the p.o. ($AUCp.o._{0-}$) studies were calculated by the method of trapezoids. The area under the first moment curve ($AUMC_{0-}$) was calculated as the product of time and drug concentration vs. time. MRT was determined as: MRT = AUMC/AUC. The total body clearance (Cl) was calculated from Cl = dose/AUCi.v. and V_{ss} was calculated using $V_{ss} = (Dosei.v.)(AUMC)/AUCi.v.^2$. The absolute bioavailability (F) was determined as the ratio (%) of the area under the curve (AUC) after p.o. dosing to that after i.v. dosing. Peak plasma concentrations (C_{max}) of roxithromycin and times to reach peak concentration (t_{max}) for the p.o. study were determined from the individual plasma concentration-time curves.

Allometric analysis

For dogs and broilers, the relationships between body weight and $t_{1/2\beta}$, MRT, V_{ss}, or Cl of roxithromycin were analyzed using data from previously published studies (12,13). Reported values for $t_{1/2\beta}$, Cl and V_{ss} were determined after intravenous (i.v.) administration of the drug.

Allometric analyses of $t_{1/2\beta}$, MRT, Cl, and V_{ss} were carried out according to the following allometric equations: $y = aW^b$, where W is the body weight; a, is the allometric coefficient and b is the allometric exponents. In each case, the pharmacokinetic parameter (y) and W were transformed logarithmically and fitted to the equation by linear least-squares regression analysis. Coefficients of determination (r^2) and P-values were calculated for each correlation.

Results

The mean plasma concentration-time curves of roxithromycin following i.v. administration of 20 mg/kg of b.w. to rats, broilers rabbit and dogs are shown in Fig 1 and comparative pharmacokinetic parameters are summarized in Table 1. For rats, variances could not be calculated because samples from different animals were pooled to determine its profiles.

The derived AUC in the animals ranged from 25.89 to 145.98 μg·h/mL (dog>>broiler, rabbit>rat). Total plasma clearance (Cl) in the animals ranged from 0.14 to 0.77 L/h/kg (rat>>broiler, rabbit>dog) and the V_{ss} ranged from 3.37 to 4.28 L/kg (dog>rat>broiler, rabbit). For the elimination from plasma after i.v. administration the MRTs were between 5.53 to 28.46 h (dog>>broiler, rabbit>rat) and elimination half-lives

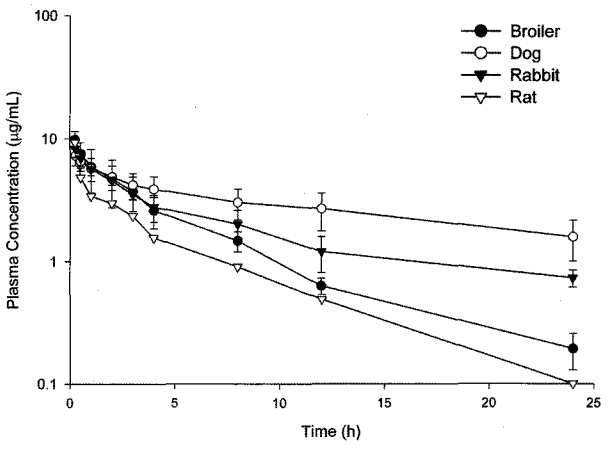

Fig 1. Plasma concentrations (mean±SD) of roxithromycin in various animal species after single intravenous administration at 20 mg/kg body weight.

Table 1. Comparative pharmacokinetic parameters (mean ± SD) of roxithromycin in various animal species after single intravenous administration with a dose rate of 20 mg/kg body weight

Parameters†	Unit	Species			
		Broiler[1]	Dog[2]	Rabbit	Rat
AUC	μg·h/mL	37.98 ± 10.00	107.34 ± 7.62	36.15 ± 6.47	25.89
α	1/h	1.52 ± 0.99	0.74 ± 0.22	0.44 ± 0.17	4.46
β	1/h	0.13 ± 0.03	0.04 ± 0.01	0.13 ± 0.02	0.15
$t_{1/2\alpha}$	h	0.81 ± 0.81	1.04 ± 0.41	1.75 ± 0.59	0.16
$t_{1/2\beta}$	h	5.83 ± 1.79	16.27 ± 2.77	5.66 ± 1.18	4.52
A	μg/L	8.53 ± 1.38	3.50 ± 0.93	5.50 ± 1.34	18.15
B	μg/L	3.50 ± 1.66	4.32 ± 1.24	2.87 ± 0.90	3.34
Cl	L/h/kg	0.55 ± 0.15	0.21 ± 0.08	0.57 ± 0.10	0.77
MRT	h	6.33 ± 0.32	22.34 ± 3.84	6.06 ± 1.05	5.53
V_{ss}	L/kg	3.47 ± 0.84	4.45 ± 1.16	3.37 ± 0.38	4.28

†AUC, area under curve; α, absorption rate constant; β, elimination rate constant; $t_{1/2\alpha}$, absorption half-life; $t_{1/2\beta}$, elimination half-life; A, intercept of absorption phase of the bi-exponential curve; B, intercept of elimination phase of the bi-exponential curve; $C_{max,}$ peak plasma concentrations; $T_{max,}$ times to reach peak concentration; Cl, total body clearance; MRT, mean residence time; V_{ss}, volume of distribution at steady-state.

[1] and [2] is data in reference 12 (Lim et al. Pharmacomkinetics of roxithromycin after intravenous administration in broilers. J Vet Clin 2006; 23: 87-90) and 13 (Lim et al. PK/PD modeling of roxithromycin for inhibitory effect of tumor necrosis factor-alpha production in dogs. J Vet Med A 2006; 54: 394-398).

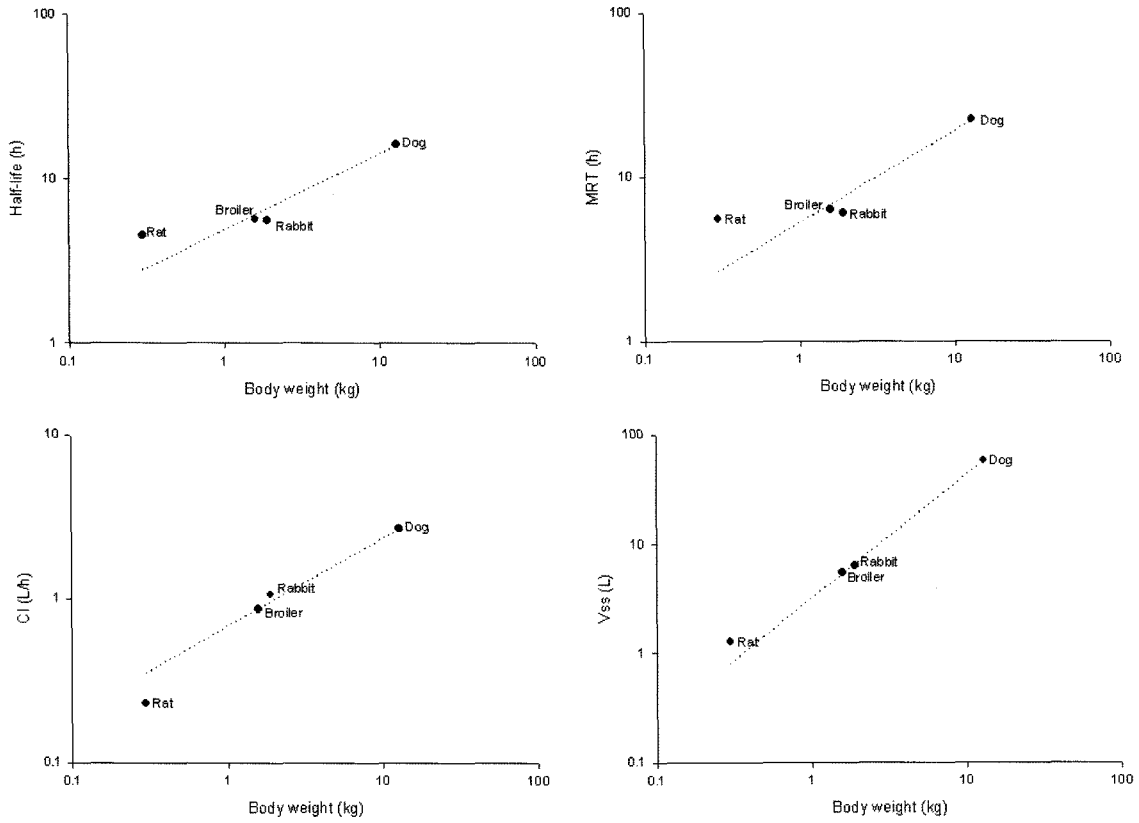

Fig 2. Allometric scaling of the pharmacokinetic parameters of roxithromycin in four different animal species. MRT, mean residence time; Cl, total body clearance; V_{ss}, volume of distribution at steady-state; half-life; $t_{1/2\beta}$, elimination half-life.

($t_{1/2\beta}$) ranged from 4.52 to 20.59 h (dog >> broiler, rabbit > rat).

Using allometric scaling, a good correlation in the allometric relationship between the different pharmacokinetic parameters and body weight for MRT ($r^2 = 0.94$), $t_{1/2\beta}$ ($r^2 = 0.97$), Cl ($r^2 = 0.99$) and V_{ss} ($r^2 = 0.99$). MRT, $t_{1/2\beta}$ Cl and V_{ss} were fitted to the following equations: $MRT = 5.24W^{0.56}$, $t_{1/2\beta} = 4.9W^{0.46}$, $Cl = 0.68W^{0.54}$ and $V_{ss} = 3.16W^{1.13}$, respectively. The values of these parameters increased with increasing body weight (Fig 2). There was a statistically significant relationship between MRT, $t_{1/2\beta}$, Cl and Vss compared with body weight ($P < 0.05$).

Discussion

Much of the focus of veterinary work has been to ascertain effective doses and dosage regimens for minor species, zoo animals, and wildlife animals based on effective doses in major veterinary species including dog, cat, horse, cow, pig, chicken, and turkey (6,7,19). Allometric relationships have been extensively explored for making interspecies comparisons of physiological parameters, such as basal metabolic rate, heart rate, organ weights, etc (2,3,5-8,19). A number of papers have examined the allometric relationships in veterinary species, including food animals (6,7,19). Recently, nonlinear mixed-effect modeling techniques have also been applied as a tool for these interspecies scaling efforts (17).

In the absence of an adequate animal model for roxithromycin, the allometric model was used to establish an empirical relationship between the pharmacokinetic parameters of roxithromycin and body weight. In general, the exponents for clearance determined by this power fit approximated the exponential value of 0.75 derived from the similarity theory (2,8). This is close to the theoretical exponent of 0.75 for scaling renal clearance in animals, as renal function is closely related to basal metabolic rate (6,19). However, derived exponential value of clearance for roxithromycin was relatively low, indicating that the kidneys provide only a minor route for roxithromycin in animals. In human data with a single dose of roxithromycin, 7 to 8% of the dose is eliminated in the urine, 50% to 55% is eliminated in the feces and 10 to 20% of the dose can be accounted for in expired CO_2 (20).

If one is looking at volume of distribution (Vd), which is a function of vascular, extracellular and total body fluid, theoretical exponent should be between 0.67 and 1.0 when if we assume that total body water directly correlates to body weight (6,19). The V_{ss} is the preferred volume of distribution estimate for studies about disposition across species because it is considered the most robust estimate of Vd as it is mathematically and physiologically independent of the elimination process (6,19). For many drugs, V_{ss} usually scales to an exponent of 1.0 (close to what we derived in this study), and Cl usually scales to an exponent of 0.75. This explains why the exponent for MRT is usually approximately 0.25, because V_{ss} is related to Cl and MRT in the following relationship: $MRT = V_{ss}/Cl$. However, in the case of our study, the exponent for Cl was actually 0.54, and the exponent for V_{ss} was 1.13. Therefore, our estimate for the exponent of MRT is 1.13-0.54 = 0.57. The actual exponent we derived from the data was 0.56 which is close to the predicted value for roxithromycin. In addition, the predicted exponent of the elimination half-life ($t_{1/2\beta} = 0.693V_\beta/Cl$) for roxith romycin was 0.46 and this value is quite different from Duthu's report that the exponents were 0.14-0.18 for allometric scaling of erythromycin, oleandomycin and tylosin (9).

The uncertainty exemplifies a weakness of empirical modeling of pharmacokinetic data-lack of fundamental insight into drug disposition. Power curves are well known for masking real differences in the data which can lead to interpretative oversimplification (9). Another weakness of any empirical model resides in the evaluation of linearity. Obtaining a good correlation of pharmacokinetic parameters to body weight does not prove the validity of the model (6,19). Using allometric scaling for roxithromycin in this study, there is a good correlation in the allometric relationship between the different pharmacokinetic parameters and body weight for MRT, $t_{1/2\beta}$, Cl and V_{ss}. Since the pharmacokinetic parameters of roxithromycin were well correlated to body weight, results of the current analyses could provide information on appropriate doses of roxithromycin for all species

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록시스로마이신의 체내동태에 대한 이종간 예측모델

임종환*, 박병권, 윤효인[1]**

*비엔씨바이오팜, 용인시, 경기도
**전진바이오, 호산동, 달서구, 대구광역시
충남대학교 수의과대학, 유성구, 대전광역시

요 약 : 본 연구에서는 랫트, 토끼, 닭, 개등의 각종 동물들의 약물동태학적 파라미터를 이용하여 록시스로마이신의 이종간 예측모델을 수립하였으며, 이때 약물동태학적 파라미터는 반감기, 청소율, 분포용적, 평균체류시간등을 이용하였다. 이종간 약물동태학적 파라미터의 변화 예측은 체중과 지수적 상관관계 ($Y=aW^b$)를 이용하였으며, 이때 Y는 약물동태학적 파라미터, W는 체중, a는 allometric coefficient를 의미한다. B는 약물동태학적 파라미터와 체중간의 상관관계를 의미하는 비례상수이다. 랫트, 토끼, 닭, 개등의 약물동태학적 파라미터인 분포용적, 청소율, 반감기, 평균체류시간등은 체중과 유의한 선형관계를 나타내었다. 본 연구에 의해 수립된 록시스로마이신에 대한 이종간 약물동태학적 파라미터의 이종간 예측모델은 다양한 종의 동물종에 대한 좀 더 정확한 용법용량을 구하는 기초자료로 이용할 수 있을 것이다.

주요어 : 록시스로마이신, 이종간 예측모델, 약물동태학