Allometric Analysis of Orbifloxacin Disposition in Nine Mammal Species: A Retrospective Analysis

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Allometric scaling is a common and well-understood technique in which quantitative relationships are established between drug disposition and physiological parameters such as body weight or organ perfusion rate [17]. It is based on the assumption that there are anatomical, physiological, and biochemical similarities among animals, which follow a pattern that can be described mathematically [4]. This kind of interspecies correlation is useful for extrapolation to animals whose access is difficult, and it has also been widely applied to predict human pharmacokinetic parameters [6]. The predictive value of allometry as a technique for interspecies scaling of drug disposition depends on selection of the appropriate pharmacokinetic parameters. Three pharmacokinetic parameters: clearance (Cl), volume of distribution (Vd), and elimination half-life (t1/2) are usually used for allometric analysis [7]. Body (systemic) clearance is the most suitable parameter for drugs that are eliminated entirely by renal excretion, whereas hepatic intrinsic clearance is generally the parameter of choice for drugs that are eliminated mainly by hepatic microsomal oxidative reactions [3].

Examples of fluoroquinolones developed exclusively for veterinary use include danofloxacin, difloxacin, enrofloxacin, and orbifloxacin, although not all of these are licensed in every country. Orbifloxacin belongs to the third generation fluoroquinolones, and is licensed for use in companion animals in many countries. The pharmacokinetics and pharmacodynamics of orbifloxacin have been investigated in various animals, including cattle, dog and rabbit [10, 11, 20]. It is well absorbed from extravascular sites with nearly complete systemic bioavailability. It is principally excreted renally, and undergoes negligible hepatic metabolism in different species, including cattle and pigs [21].

The allometric analyses of pharmacokinetic parameters of danofloxacin, difloxacin, enrofloxacin and its metabolite ciprofloxacin, marbofloxacin, pefloxacin and its metabolite norfloxacin have been performed across different species [5, 7, 8, 15]. However, there was no adequate information for orbifloxacin to perform similar analysis. In the past few years, the pharmacokinetics of orbifloxacin has been reported in several species. This prompted us to assess the relationship between the main pharmacokinetic parameters and body weight (W) across mammal species for this valuable drug, and to determine the scaling coefficients in those cases where significant relationships are found.

Pharmacokinetic data of nine mammal species, including cattle, dog, rat, rabbit, goat, camel horse, cat and sheep were obtained from previously published studies (Table 1). Values for total body clearance, apparent volume of distribution at steady state (Vss) and t1/2 were obtained after intravenous administration of the drug. Data for W were obtained from these studies. When a range of W was given, mean values were used. Analyses did not consider the influence of age, sex or physiological state of the animals. The matrices of interest were serum or plasma. In all animals, except sheep, antibiotic concentrations were measured by high performance liquid chromatography. Drug concentrations in sheep were measured using bioassay, which could not distinguish between the parent drug and active metabolites. The decision to include these data in our analysis was based...
on two reasons: first, studies in animals, including cattle and pig, indicated that orbifloxacin undergoes very minimal metabolism (<5%) [21], and second, we observed no substantial differences in the values computed with or without pharmacokinetic parameters of sheep.

Regression analysis of logarithmic values for W, Cl, Vss or \( t_{1/2} \) was performed using SAS software (SAS Institute, Cary, NC, U.S.A.). The pharmacokinetic parameter (Y) and W were transformed logarithmically and fitted to the equation:

\[
\log Y = c + b \log W
\]

Where \( Y \) is the parameter of interest, \( W \) is the body weight, and \( b \) and \( c \) are the slope and the intercept, respectively. The following allometric equation was then applied:

\[
Y = a W^b
\]

Where \( a \) is the antilogarithm of \( c \). Double logarithmic plots of \( W \) vs. Cl, Vss or \( t_{1/2} \) were constructed. Coefficients of determination \((r^2)\) and \( P \)-values were calculated for each correlation.

The allometric relationship between the different pharmacokinetic parameters and \( W \) is shown in Fig. 1. Regression of \( \log \ Cl \) versus \( \log W \) produced an equation (\( \log \ Cl = 1.03 \log W + 0.643 \)), which showed a good correlation with a \( r^2 \) of 0.95 (\( P<0.001 \)). A good correlation with \( W \) was also observed for Vss. The equation of the line was \( \log Vss = 1.05 \log W + 0.04 \), and the value of \( r^2 \) was 0.99 (\( P<0.001 \)). However, orbifloxacin \( t_{1/2} \) was not related to \( W \) (\( \log t_{1/2} =0.01 \log W + 0.612; r^2= 0.01; P=0.835, \text{non-significant}) \). Our estimates (\( Cl=4.40 \ W^{1.03} \); \( Vss=1.10 \ W^{1.05} \)) indicate that the increase in these parameters with \( W \) approximates a linear power relationship with slopes being very close to one. Best results of the allometric analysis are generally expected when the drug obeys first order kinetics in all the species studied, its percentage of protein binding is linear over the concentration range commonly used, and the elimination process is renal or biliary [18]. Accordingly, we found a best correlation between Cl and Vss with \( W \) for orbifloxacin, which is primarily excreted renally and has a very minimal binding to plasma proteins in many species, including cattle and camels [10, 13]. The exponents of orbifloxacin between \( \log Cl \) or \( \log Vss \) and \( W \) were similar to the values reported for marbofloxacin [7, 15]. However, both values were higher than those reported for other fluoroquinolones,

Table 1. Pharmacokinetic parameters of orbifloxacin after intravenous administration to nine mammal species\(^a\)

<table>
<thead>
<tr>
<th>Species</th>
<th>Sample size</th>
<th>W (kg)</th>
<th>Dose (mg/kg)</th>
<th>Cl (ml/min/kg)</th>
<th>Vss (l/kg)</th>
<th>( t_{1/2} ) (hr)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goat</td>
<td>6</td>
<td>54.15</td>
<td>2.5</td>
<td>6.67</td>
<td>1.13</td>
<td>4.12</td>
<td>[19]</td>
</tr>
<tr>
<td>Horse</td>
<td>6</td>
<td>450.00</td>
<td>2.5</td>
<td>4.67</td>
<td>1.58</td>
<td>5.08</td>
<td>[9]</td>
</tr>
<tr>
<td>Rabbit</td>
<td>6</td>
<td>4.40</td>
<td>5</td>
<td>15.10</td>
<td>1.71</td>
<td>2.50(^b)</td>
<td>[20]</td>
</tr>
<tr>
<td>Camel</td>
<td>6</td>
<td>432.50</td>
<td>2.5</td>
<td>3.83</td>
<td>1.73</td>
<td>5.74</td>
<td>[13]</td>
</tr>
<tr>
<td>Cow</td>
<td>6</td>
<td>464.50</td>
<td>3</td>
<td>4.00</td>
<td>0.92</td>
<td>3.20</td>
<td>[10]</td>
</tr>
<tr>
<td>Dog</td>
<td>12</td>
<td>0.33</td>
<td>5</td>
<td>5.17</td>
<td>1.61</td>
<td>4.23</td>
<td>[12]</td>
</tr>
<tr>
<td>Cat(^c)</td>
<td>12</td>
<td>4.00</td>
<td>2.5</td>
<td>0.24</td>
<td>1.30</td>
<td>4.50</td>
<td>[24]</td>
</tr>
<tr>
<td>Sheep</td>
<td>6</td>
<td>50.00</td>
<td>2.5</td>
<td>0.32</td>
<td>1.35</td>
<td>3.16</td>
<td>[14]</td>
</tr>
</tbody>
</table>

\( a \) Unless otherwise stated, data represent the mean values for all parameters. \( b \) Harmonic mean. \( c \) Values are also based on manufacturer's data: http://sploughus.naccvp.com.
such as enrofloxacin, ciprofloxacin and difloxacin [5, 8, 15]. Metabolism has minimal effect on the elimination of both orbifloxacin and marbofloxacin, which are mainly eliminated by renal route [1, 21]. This may partly account for the higher exponents of the allometric equation in both orbifloxacin and marbofloxacin, compared to those fluoroquinolones which undergo significant hepatic metabolism and eliminated in both urine and feces. Hence, it has already been suggested that allometric scaling could have some limitations in predicting the pharmacokinetics of fluoroquinolones which are partly metabolized and partly excreted renally, because the rate of the two elimination processes could be different in different species [7, 18]. The t_{1/2} of orbifloxacin was allometrically related to W with an exponent of 0.01. This is consistent with the reported low degree of correlation of t_{1/2} with W for other veterinary fluoroquinolones [7, 8, 15]. Half-life is a hybrid pharmacokinetic parameter scaling to V_d/Cl, therefore either of these variables could be the cause of the small allometric exponent of t_{1/2} [7].

Intra-species variations in fluoroquinolone pharmacokinetic parameters have been reported in animals of different age, sex, breed or physiological state. These include differences in ciprofloxacin metabolism between male and female rats, effect of lactation in rabbits on the binding of ciprofloxacin to plasma proteins, and longer enrofloxacin t_{1/2} values for the foal and the young camel than the horse or mature camel [2, 8, 23]. Our analyses did not consider the influence of age, sex or physiological state of the animals due to the paucity of published information for orbifloxacin involving animals in different conditions. However, most pharmacokinetic data included in our study were derived from adult animals. This could minimize the potential differences in pharmacokinetic parameters of animals due to age-dependent maturity of renal function and metabolic capacity of liver [7]. Furthermore, orbifloxacin had minimal protein binding in many species [10, 13], and showed good tissue penetration in both non-lactating and lactating animals such as ewes, does and camels [13, 14, 19]. These may have contributed to the observed good correlation for orbifloxacin between CI or V_s and W of animals.

Some previous studies have emphasized the importance of dividing animal species in groups according to their physiological characteristics, for instance, analyzing data for mammals and birds separately, to improve the predictive power of allometric scaling [15, 18]. To test the influence of including data from bird species on the allometric parameters obtained using mammals, we performed analyses by including a pharmacokinetic data of orbifloxacin in Japanese quail (Coturnix japonica) reported recently during the review process of our study [16]. The exponents of orbifloxacin between log CI or log V_s and W were almost similar with or without the data for Japanese quail (data not shown), indicating a reasonably good prediction of pharmacokinetic parameters for orbifloxacin irrespective of the animal species involved.

In conclusion, this study demonstrated that interspecies scaling of orbifloxacin pharmacokinetics is possible across species. Elimination half-life is independent of W, whereas Cl and V_d can be extrapolated using allometric equations. This would be useful to predict orbifloxacin disposition in species that have not been studied.

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REFERENCES


