Pharmacokinetic characteristics and tissue residues for marbofloxacin and its metabolite N-desmethyl-marbofloxacin in broiler chickens

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Objectives—To determine pharmacokinetic characteristics of marbofloxacin after a single IV and oral administration and tissue residues after serial daily oral administration in chickens.

Animals—40 healthy broiler chickens.

Procedure—Two groups of chickens (groups A and B; 8 chickens/group) were administered a single IV and oral administration of marbofloxacin (2 mg/kg). Chickens of group C (n = 24) were given serial daily doses of marbofloxacin (2 mg/kg, PO, q 24 h for 3 days). Plasma (groups A and B) and tissue concentrations (group C) of marbofloxacin and its major metabolite N-desmethyl-marbofloxacin were determined by use of high-performance liquid chromatography. Residues of marbofloxacin and N-desmethyl-marbofloxacin were measured in target tissues.

Results—Elimination half-life and mean residence time of marbofloxacin in plasma were 5.26 and 4.36 hours after IV administration and 8.69 and 8.55 hours after oral administration, respectively. Maximal plasma concentration was 1.05 µg/ml, and interval from oral administration until maximum concentration was 1.48 hours. Oral bioavailability of marbofloxacin was 56.82%. High concentrations of marbofloxacin and N-desmethyl-marbofloxacin were found in the kidneys, liver, muscles, and skin plus fat 24 hours after the final dose of marbofloxacin; however, marbofloxacin and N-desmethyl-marbofloxacin were detected in only hepatic (27.6 and 98.7 µg/kg, respectively) and renal (39.7 and 69.1 µg/kg, respectively) tissues 72 hours after termination of marbofloxacin treatment.

Conclusions and Clinical Relevance—Analysis of pharmacokinetic data obtained in this study reveals that a minimal therapeutic dose of 2 mg/kg, PO, every 24 hours should be appropriate for control of most infections in chickens. (Am J Vet Res 2002; 63:927–933)

Marbofloxacin is a fluorinated quinolone introduced for exclusive use in veterinary medicine.1-12 Similar to other fluoroquinolones, marbofloxacin achieves rapid bactericidal activity by inhibiting bacterial DNA gyrase, an enzyme responsible for packaging DNA within cells.5,6 Fluoroquinolones labeled for veterinary use share high antimicrobial activity in vitro against a wide number of gram-negative and some gram-positive bacteria, low plasma protein binding, large volume of distribution with good concentrations in tissues and body fluids, good penetration into phagocytic cells, and activity at extremely low concentrations.5,6,13 Marbofloxacin has been used in the treatment of bacterial diseases of various organ systems, particularly skin and ear infections caused by Staphylococcus intermedius and Pseudomonas aeruginosa,14,15 urinary tract infections caused mainly by aerobiotic bacteria such as Escherichia coli, Enterobacter spp, Pseudomonas spp, and Staphylococcus spp,16 and respiratory tract diseases caused mainly by Mycoplasma hyopneumoniae, Pasteurella multocida, and Actinobacillus pleuropneumoniae.17-19 Moreover, marbofloxacin seems to be suitable for use in the prevention of postsurgical infections.19

Following oral administration, marbofloxacin is rapidly absorbed and efficiently distributed to tissues in dogs and sows.20,21 It readily crosses the blood-milk barrier in the udder of cows and ewes22 and has a relatively prolonged elimination half-life in several species of animals. In dogs,22 the drug is transformed in the liver into 2 main metabolites, N-desmethyl-marbofloxacin and N-oxide-marbofloxacin (Fig 1). Approximately 40% of the dose is excreted unchanged in the urine as marbofloxacin.

Marbofloxacin has clinical application for use in small animals with dermatologic, urinary tract, digestive tract, and respiratory tract infections. Marbofloxacin also may constitute an effective alternative drug for use in treating food-producing animals with bacterial infections. In the European Union, marbofloxacin is approved for oral or parenteral administration to cattle (including lactating dairy cattle) and pigs with respiratory tract diseases and for parenteral administration to sows with mastitis-metritis-agalactiae syndrome. Maximum residue limits (MRL) of 150 µg/kg for muscle, liver, and kidney and 50 µg/kg for fat and skin in cattle and pigs (expressed as the parent compound marbofloxacin) have been established.23 Antimicrobial properties of marbofloxacin may be advantageous for use in poultry. Limited information is available on disposition, metabolism, and safety of marbofloxacin in birds.24 Therefore, the objectives of
tilled water to achieve a total volume of 0.5 ml for IV admin-

Materials and Methods

the study reported here were to investigate plasma dis-

Materials and Methods

Animals—Forty healthy Ross male broiler chickens that

Experimental design—Chickens were randomly allotted
to 3 groups. Groups A and B (8 chickens/group) were used to investigate pharmacokinetic charac-
teristics of marbofloxacin after a single IV and oral administra-
tion, respectively. The dosage used for the single administra-
tions was 2 mg/kg. Chickens of group C (n = 24) were used
to study tissue residues of marbofloxacin and its metabolites.
Chickens of group C were given serial daily doses of mar-
bofloxacin (2 mg/kg, PO, q 24 h for 3 consecutive days). All
doses were administered between 8 and 9 AM.

Marbofloxacin chlorhydrate was dissolved in sterile dis-
tilled water to achieve a total volume of 0.5 ml for IV admin-
istration or 2 ml for oral administration. Marbofloxacin was
administered IV into the right brachial vein of chickens in
group A or was administered directly into the crop of chick-
ens of groups B and C by use of a thin plastic tube attached
to a syringe. Food but not water was withheld from 12 hours
before until 6 hours after drug administration.

Blood samples (0.5 to 1 ml/sample) were collected from
the left brachial vein of each chicken of groups A and B.
Samples were collected into heparinized syringes through a
 cannula immediately before (time 0) and 10, 20, and 30
minutes and 1, 2, 4, 6, 8, 12, and 24 hours after drug admin-
istration. Blood samples were centrifuged (1,800 × g for 10
minutes), and plasma was harvested and stored frozen at −45
C until analyzed.

Marbofloxacin concentrations were measured in plasma
samples of chickens in group A. Plasma samples of chickens
in group B were assayed for marbofloxacin, N-desmethyl-
marbofloxacin, and N-oxide-marbofloxacin.

Chickens of group C were euthanatized by use of carbon
dioxide 24, 48, 72, and 120 hours after the last dose of mar-
bofloxacin was administered. Six chickens were euthanatized
at each time point. Birds were immediately exsanguinated,
and blood samples and tissue specimens (2 g) of kidneys,
liver, muscles, and skin plus fat were obtained. Each of the
tissue specimens was carefully weighed and stored frozen at
−45 C until assayed for concentrations of marbofloxacin,
N-desmethyl-marbofloxacin, and N-oxide-marbofloxacin.

Drug assay—Plasma and tissue concentrations of mar-
bofloxacin, N-desmethyl-marbofloxacin, and N-oxide-mar-
bofloxacin were measured by use of a high-performance liq-
uid chromatography (HPLC) method reported by Schneider
et al with modifications. Plasma and homogenized kidney,
liver, muscle, and skin plus fat specimens were extracted sep-
ately in 3 aliquots of chloroform (5 ml) and 0.1

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uid chromatography (HPLC) method reported by Schneider
et al with modifications. Plasma and homogenized kidney,
liver, muscle, and skin plus fat specimens were extracted sep-
ately in 3 aliquots of chloroform (5 ml) and 0.1M sodium
phosphate buffer, pH 7.4 (3 ml). After shaking and centrifu-
gation (1,800 × g for 10 minutes), the organic phases from
the 3 extractions of each specimen were pooled and dried
under nitrogen at 30 C. The residue was dissolved in 0.5 ml
of the mobile phase before HPLC analysis. Twenty microliters
of this solution was injected into the HPLC system, which
was equipped with a reverse-phase column (particle size, 5
µm; inside diameter, 12.2 X 4 mm). The mobile phase consist-
ed of a mixture of methanol:acetonitrile:buffer ( pH 2.7):acetic
acid:triethylamine (10:2.86:1:1 [vol:vol]). The buffer was prepared from a 0.4% aqueous solution of tetrabutylammoni-
unum hydrogen sulfate (approx 100 ml). Elution flow rate was
1 ml/min. Column eluate was monitored by use of a UV
detector at a wavelength of 295 nm and a data processor.

Peak areas in chromatograms of the samples were quantitat-
ed, using the external-standard technique, by use of solutions
of marbofloxacin, N-desmethyl-marbofloxacin, and N-oxide-
marbofloxacin reference standards.

For plasma and tissue specimens, standard curves were
linear for concentrations ranging from 0.01 to 20 µg/ml of
plasma (2.5 to 5,000 µg/kg of tissue) for marbofloxacin,
N-desmethyl-marbofloxacin, and N-oxide-marbofloxacin.

Intra- and interassay coefficients of variation were < 5.7%.

For plasma and tissue specimens, an injection volume of 20 µl
provided quantitation limits of 0.01 µg/ml for marbofloxacin,
N-desmethyl-marbofloxacin, and N-oxide-marbofloxacin.

In plasma samples, mean analytical recovery was 84% for mar-
bofloxacin, N-desmethyl-marbofloxacin, and N-oxide-marbofloxacin. In tissue specimens, overall recovery was > 70% for marbofloxacin, N-desmethyl-marbofloxacin, and N-oxide-marbofloxacin. The method used was selective for the substances analyzed; endogenous interference was not observed on chromatograms.

Figure 1—Structures of marbofloxacin and its metabolites
N-desmethyl-marbofloxacin, and N-oxide-marbofloxacin.
Data analysis—Plasma concentration-versus-time data were sequentially fitted to 1-, 2-, and multiple-compartment models. The model of best fit was selected on the basis of Akaike information criteria as well as criteria reported by Schwartz. The 2-compartment model was the best fit for the data of all chickens, and this model was used to establish pharmacokinetic characteristics. Plasma concentration-versus-time curves of marbofloxacin after a single IV and oral administration and those of N-desmethyl-marbofloxacin (the main metabolite in plasma) after a single oral administration of marbofloxacin were obtained for each chicken and were fitted to the following exponential equations for IV and oral administration, respectively:

\[ C(t) = C_0 \cdot e^{-\alpha t} + C_1 \cdot e^{-\beta t} \]

where \( C(t) \) is the plasma concentration of the drug calculated for each time value \( t \); \( C_0 \), \( C_1 \), and \( C_2 \) are mathematical coefficients; \( \alpha \) is the hybrid rate constant for the distribution phase; \( \beta \) is the hybrid rate constant for the elimination terminal phase; and \( K_1 \) is the first-order absorption rate constant.

Absorption half-life (\( t_{1/2a} \)), half-life of the \( \beta \) phase (\( t_{1/2\beta} \)), distribution rate constants for transfer of the drug from the peripheral to the central compartment (\( K_{21} \)), distribution rate constant for transfer of the drug from the central to the peripheral compartment (\( K_{12} \)), and the elimination rate constant (\( K_{a} \)) were calculated by use of standard equations as described elsewhere.

Mean residence time (MRT) was calculated by use of the following equation for IV and oral administration, respectively:

\[ MRT_{IV} = \left( \frac{A_1}{\alpha} + \frac{A_2}{\beta} \right) \cdot \left( \frac{1}{AUC_{IV}} \right) \]
\[ MRT_{oral} = \left( \frac{A_1}{\alpha} + \frac{A_2}{\beta} \right) \cdot \left( \frac{1}{AUC_{oral}} \right) \]

Oral bioavailability (F) was determined by use of the following equation:

\[ F = \frac{AUC_{oral}}{AUC_{IV}} \]

Oral bioavailability was determined directly from the concentration-versus-time curve.

Mean absorption time (MAT) was calculated by use of the following equation:

\[ MAT = MRT_{oral} - MRT_{IV} \]

Oral clearance (CLoral) was calculated by use of the following equation:

\[ CL_{oral} = \left( \frac{dose/kg}{AUC_{oral}} \right) \]

Total plasma clearance (CLT) was calculated by use of the following equation:

\[ CL_T = \left( \frac{dose/kg}{AUC_{IV}} + \frac{dose/kg}{AUC_{oral}} \right) \cdot \left( \frac{F}{AUC} \right) \]

Apparent volume of distribution (\( Vd_{area} \)) was determined by use of the following equation for IV and oral administration, respectively:

\[ Vd_{area IV} = \left( \frac{dose/kg}{AUC_{IV}} \right) \cdot \left( \frac{1}{F/AUC} \right) \]
\[ Vd_{area oral} = \left( \frac{dose/kg}{AUC_{oral}} \right) \cdot \left( \frac{1}{F/AUC} \right) \]

Maximum plasma concentration of drug (\( C_{MAX} \)) after oral administration and the time at which \( C_{MAX} \) was achieved (\( T_{MAX} \)) were determined directly from the concentration-versus-time curve.

Results

Plasma disposition of marbofloxacin—Mean plasma concentrations of marbofloxacin obtained after IV administration and plasma disposition of marbofloxacin and N-desmethyl-marbofloxacin after oral administration of marbofloxacin were determined (Fig 2). The plasma concentration-versus-time patterns for marbofloxacin after IV administration and for marbofloxacin and N-desmethyl-marbofloxacin after oral administration of marbofloxacin for each chicken were similar to the overall means. Analysis of plasma concentration-versus-time curves indicated a biphasic decrease after oral and IV administration. Data best fit a 2-compartment open model. Values of kinetic variables

![Figure 2](image-url)
that described absorption and disposition kinetics of marbofloxacin in chickens were determined (Table 1).

After IV administration of marbofloxacin, a rapid distribution phase (mean ± SD t1/2α, 0.12 ± 0.02 hour) and a slower elimination phase (mean t1/2β, 5.26 ± 0.66 hour) were observed (Fig 2; Table 1). Mean Vdarea and Vdss values were 1.33 ± 0.33 and 0.77 ± 0.25 L/kg, respectively, and mean CLT was 1.17 ± 0.03 L/h/kg. When administered orally, the drug was rapidly but only partially absorbed. Drug concentrations in plasma 10 and 20 minutes after oral administration of marbofloxacin (2 mg/kg) were 0.18 ± 0.02 and 0.36 ± 0.08 µg/ml, and plasma drug concentrations exceeded 0.2 µg/ml (mean, 0.22 ± 0.04 µg/ml) for 8 hours. Value for t1/2α was 0.60 ± 0.05 hours. Bioavailability of marbofloxacin after oral administration was 56.82%. The CMAX of marbofloxacin (1.05 ± 0.15 µg/ml) was detected 1.48 ± 0.09 hours after oral administration. The MAT after oral administration was 4.19 hours.

A fraction of marbofloxacin was metabolized to N-desmethyl-marbofloxacin after oral administration of marbofloxacin. This metabolite represented 67.8% of the parent drug plasma concentrations, as calculated by use of the ratio between mean AUC for marbofloxacin and N-desmethyl-marbofloxacin after oral administration of marbofloxacin at the rate of 2 mg/kg, every 24 hours, for 3 days.

Table 1—Pharmacokinetic characteristics of marbofloxacin for 8 chickens after a single IV and oral administration of marbofloxacin (2 mg/kg)

<table>
<thead>
<tr>
<th>Variable</th>
<th>IV</th>
<th>Oral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable</td>
<td>Range</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td>t1/2α (h)</td>
<td>1.14–2.10</td>
<td>1.45 ± 0.29</td>
</tr>
<tr>
<td>t1/2β (h)</td>
<td>7.70–11.74</td>
<td>9.60 ± 1.43</td>
</tr>
<tr>
<td>t2/3β (h)</td>
<td>0.09–0.22</td>
<td>0.16 ± 0.04</td>
</tr>
<tr>
<td>K10 (h)</td>
<td>0.10–0.15</td>
<td>0.12 ± 0.01</td>
</tr>
<tr>
<td>K12 (h)</td>
<td>0.17–0.34</td>
<td>0.28 ± 0.05</td>
</tr>
<tr>
<td>AUC (mg/h/L)</td>
<td>3.10–5.71</td>
<td>4.55 ± 0.67</td>
</tr>
<tr>
<td>MRT (h)</td>
<td>6.63–12.37</td>
<td>9.64 ± 1.85</td>
</tr>
<tr>
<td>CMAX (µg/ml)</td>
<td>0.37–0.99</td>
<td>0.67 ± 0.19</td>
</tr>
<tr>
<td>Tmax (h)</td>
<td>1.37–2.12</td>
<td>1.60 ± 0.22</td>
</tr>
</tbody>
</table>

See Table 1 for key.

Table 2—Pharmacokinetic characteristics of N-desmethy-lmarbofloxacin after a single oral administration of marbofloxacin (2 mg/kg) to 8 chickens

<table>
<thead>
<tr>
<th>Variable</th>
<th>Range</th>
<th>Mean ± SD</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>t1/2α (h)</td>
<td>0.65–1.27</td>
<td>0.88 ± 0.20</td>
<td>—</td>
</tr>
<tr>
<td>α (h)</td>
<td>4.49–6.0</td>
<td>5.46 ± 0.61</td>
<td>3.83</td>
</tr>
<tr>
<td>β (h)</td>
<td>0.11–0.16</td>
<td>0.13 ± 0.02</td>
<td>0.13</td>
</tr>
<tr>
<td>Ka (h)</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>t1/2α (h)</td>
<td>0.11–0.15</td>
<td>0.12 ± 0.02</td>
<td>0.18</td>
</tr>
<tr>
<td>t1/2β (h)</td>
<td>5.33–6.30</td>
<td>5.26 ± 0.86</td>
<td>5.33</td>
</tr>
<tr>
<td>t2/3β (h)</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Vdarea (L/kg)</td>
<td>0.80–1.82</td>
<td>1.33 ± 0.33</td>
<td>1.45</td>
</tr>
<tr>
<td>Vdss (L/kg)</td>
<td>0.41–1.14</td>
<td>0.77 ± 0.25</td>
<td>0.76</td>
</tr>
<tr>
<td>Ka (h)</td>
<td>2.00–2.98</td>
<td>2.85 ± 0.57</td>
<td>1.75</td>
</tr>
<tr>
<td>K10 (h)</td>
<td>1.94–3.03</td>
<td>2.44 ± 0.36</td>
<td>1.95</td>
</tr>
<tr>
<td>K12 (h)</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>AUC (mg/h/L)</td>
<td>10.50–15.60</td>
<td>11.81 ± 2.21</td>
<td>10.61</td>
</tr>
<tr>
<td>MRT (h)</td>
<td>3.26–5.80</td>
<td>4.36 ± 0.80</td>
<td>4.03</td>
</tr>
<tr>
<td>CLT (L/h/kg)</td>
<td>0.13–0.23</td>
<td>0.17 ± 0.03</td>
<td>0.19</td>
</tr>
<tr>
<td>CMAX (µg/ml)</td>
<td>0.75–1.10</td>
<td>0.95 ± 0.15</td>
<td>1.04</td>
</tr>
<tr>
<td>Tmax (h)</td>
<td>1.31–1.58</td>
<td>1.48 ± 0.09</td>
<td>1.52</td>
</tr>
</tbody>
</table>

Table 3—Mean ± SEM plasma and tissue concentrations of marbofloxacin and N-desmethyl-marbofloxacin for chickens orally administered marbofloxacin at the rate of 2 mg/kg, every 24 hours, for 3 days

<table>
<thead>
<tr>
<th>Source</th>
<th>Time after last dose (d)</th>
<th>Marbofloxacin</th>
<th>N-desmethyl-marbofloxacin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma</td>
<td></td>
<td></td>
<td>0.047 ± 0.003</td>
</tr>
<tr>
<td>Kidneys</td>
<td>1</td>
<td>985.1 ± 71.7</td>
<td>499.0 ± 59.9</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>420.4 ± 47.6</td>
<td>163.9 ± 31.9</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>39.7 ± 4.26</td>
<td>98.1 ± 12.5</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>7.4 ± 2.4</td>
<td>21.7 ± 4.9</td>
</tr>
<tr>
<td>Liver</td>
<td>1</td>
<td>735.0 ± 45.1</td>
<td>553.8 ± 85.6</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>342.7 ± 38.0</td>
<td>157.9 ± 30.0</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>27.6 ± 9.9</td>
<td>98.7 ± 14.7</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>10.5 ± 1.5</td>
<td>51.3 ± 7.6</td>
</tr>
<tr>
<td>Muscle</td>
<td>1</td>
<td>32.5 ± 3.3</td>
<td>119.1 ± 13.6</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>18.4 ± 3.0</td>
<td>112.6 ± 22.5</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Skin plus fat</td>
<td>1</td>
<td>42.9 ± 5.9</td>
<td>268.5 ± 51.5</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>10.4 ± 1.8</td>
<td>54.9 ± 10.0</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>ND</td>
<td>ND</td>
</tr>
</tbody>
</table>

Each value is the mean ± SD for 6 chickens. ND = Not detectable.
oral administration in chickens was best described by chickens. Disposition of marbofloxacin after IV and bofloxacin (2 mg/kg) were determined in healthy infectious diseases (coli bacillosis, airsacculitis, en, marbofloxacin would be useful to control com- of marbofloxacin in food-producing animals. In chick- by bacteria.

Few reports are available on the pharmacokinetics of marbofloxacin after oral administration of marbofloxacin. The other metabolite (N-oxide-marbofloxacin) could not be detected in plasma. Mean plasma concentration of N-desethyl-marbofloxacin (0.67 ± 0.19 µg/ml) peaked at 1.60 ± 0.22 hours after oral administration of marbofloxacin. Mean t1/2β of N-desethyl-marbofloxacin after oral administration of marbofloxacin was 9.90 ± 1.43 hours (Fig 2; Table 2). Mean CLa for the entire drug (marbofloxacin and N-desethyl-marbofloxacin) was 0.18 ± 0.02 L/h/kg.

Analysis of tissue residues—None of the chick- ens had treatment-related adverse effects during the study. Residues of marbofloxacin, N-desethyl-marbofloxacin, and N-oxide-marbofloxacin in plasma and tissue specimens after daily oral administration of marbofloxacin (2 mg/kg for 3 consecutive days) were determined. Marbofloxacin was metabolized exten- sively to N-desethyl-marbofloxacin. We did not detect N-oxide-marbofloxacin in tissues. One day after the final daily dose was administered, mean plasma concentration of marbofloxacin was 0.047 ± 0.003 µg/ml (Table 3). This value was similar to that obtained after oral administration of a single dose (0.046 ± 0.006 µg/ml). Mean tissue concentrations of marbofloxacin and N-desethyl-marbofloxacin ranged between 32 and 985 µg/kg 1 day after administration of the final dose. Marbofloxacin and N-desethyl-marbofloxacin were detected only in hepatic (27.6 ± 6.9 and 98.7 ± 14.7 µg/kg, respectively) and renal (39.7 ± 4.2 and 69.1 ± 12.5 µg/kg, respectively) tissues 72 hours after termination of marbofloxacin treatment.

Discussion

Fluoroquinolone antibiotics provide an important option for empiric treatment of life-threatening gram- negative infections or for use in situations in which microbial culture and susceptibility testing indicate that they will be effective for treatment of severe or recurrent infections in the urinary tract, skin, or soft tissues. Improper use of these agents can potentially lead to bacterial resistance, which could result in removal from the veterinarian’s arsenal of antimicrobial compounds. Therefore, pharmacokinetic characteristics of these antibiotics combined with microbiologic susceptibility patterns should be considered in the choice of treatment regimens that maximize efficacy and minimize development of antimicrobial resistance by bacteria.

Few reports are available on the pharmacokinetics of marbofloxacin in food-producing animals. In chick- ens, marbofloxacin would be useful to control common infectious diseases (coli bacillosis, airsacculitis, infections attributable to Staphylococcus spp, omphali- tis, and infection with M gallisepticum). In the study reported here, pharmacokinetics of marbofloxacin after a single IV and oral administration (2 mg/kg) as well as the pharmacokinetics of N-desethyl-marbofloxacin after a single oral administration of marbofloxacin (2 mg/kg) were determined in healthy chickens. Disposition of marbofloxacin after IV and oral administration in chickens was best described by use of a 2-compartment model. Disappearance of marbofloxacin from the plasma of chickens was characterized by an initial rapid distribution phase followed by a slower elimination phase. The t1/2β of marbofloxacin is shorter in chickens (5.26 hours after IV administration) than in dogs (10.8 hours),22 but it is longer than in lactating cows (2.2 hours).21 The t1/2β of 5.26 hours in chickens was similar to that reported for lactating sows20 and Eurasian buzzards.24 The t1/2β of marbofloxacin increased by 65% (to a value of 8.69 hours) after oral administration. The Vd(area) (2.15 L/kg) indicated that marbofloxacin easily penetrated all tissues in chickens, which is in agreement with data reported for other fluoroquinolones.31,32

When given orally, marbofloxacin was rapidly and efficiently absorbed in chickens. Marbofloxacin has a TMAX in chickens (1.48 hours after oral administration) similar to that reported for other animals (range, 1.57 to 1.97 hours).22,23 Mean CMAX (1.03 ± 0.15 µg/ml) in the study reported here was comparable to that of stud- ies in which marbofloxacin administered orally at the same dosage of 2 mg/kg yielded a CMAX of 0.89 µg/ml in sows20 and 1.37 µg/ml in dogs.32 Oral bioavailability of marbofloxacin was 56.82% in chickens of our study, which was lower than the F of 77.95% for lactating sows.20 Nevertheless, in our study in which we used the highest AUCoral/lowest AUCIV and the lowest AUCoral/highest AUCIV, the F of marbofloxacin ranged from 40 to 80%. The relatively low F for marbofloxacin in chickens also may have been caused by biliary excretion or extensive metabolism of the drug (ie, first-pass metabolism). In mammalian species, the metabo- lism of marbofloxacin has still not been fully elucidated, although the piperazinyl ring seems to be the center of metabolism. In dogs, 2 metabolites of marbofloxacin (N-oxide-marbofloxacin and N-desethyl- marbofloxacin) have been detected (Fig 1), with N-oxide-marbofloxacin being the major metabolite resulting from hepatic biotransformation of mar- bofloxacin in dogs.25 However, this metabolite was not detected in the chickens reported here (limit of detection for the HPLC analysis, 0.04 µg/ml). In our study, chickens metabolized marbofloxacin to N-desethyl- marbofloxacin. Marbofloxacin administered orally in our study resulted in a maximal N-desethyl-mar- bofloxacin concentration in plasma of 0.67 ± 0.19 µg/ml. Demethylated metabolites of gyrase inhibitors are microbiologically active, and it currently is not known whether these metabolites have any other actions in the body.

Fluoroquinolones are excreted by renal, biliary, or hepatic metabolic pathways; renal tubular secretion appears to be involved in renal excretion.3 The amounts of marbofloxacin and N-desethyl-marbofloxacin excreted in urine were not determined in the study reported here. Approximately 40% of marbofloxacin is excreted as unchanged drug in the urine of dogs.19 Our results revealed that N-desethyl-marbofloxacin accounted for 67.8% of the parent drug plasma concentrations, which would suggest that approximately 30% of marbofloxacin is excreted primarily as unchanged parent drug in the urine of chickens. It is generally accepted that fluoroquinolones act

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The next step is to define the withdrawal time necessary for therapeutic purposes to food-producing animals. Metabolites in edible tissues when it is administered to know about the persistence of a drug and its metabolites. From a public health viewpoint, it is important except for Spp. With the oral dose of marbofloxacin except for Salmonella resistant to fluoroquinolones. Resistance to fluoroquinolones is a CMAX-to-MIC ratio ≥ 10 or an AUC-to-MIC ratio ≥ 125.4-5 Marbofloxacin has excellent potency in vitro against most pathogens that affect poultry.5,11,28 The MIC50 of marbofloxacin are generally ≤ 0.20 µg/ml for gram-negative bacteria, except for P aeruginosa.4 In chickens, oral administration of marbofloxacin results in potentially therapeutic plasma concentrations against gram-negative bacterial pathogens such as E coli, P multocida, and Salmonella spp. With the oral dose of marbofloxacin used in our study (ie, 2 mg/kg), a CMAX-to-MIC50 ratio of 5.25 and an AUC-to-MIC50 ratio of 33.55 (calculated by use of an MIC50 value of 0.20 for general pathogens) may be anticipated. However, by use of the MIC50 value of 0.025 µg/ml for the bacterial pathogens E coli and P multocida,4 a single oral dose of marbofloxacin (2 mg/kg) yielded a CMAX-to-MIC50 ratio of 42 and an AUC-to-MIC50 ratio of 268. On the basis of results of this study, marbofloxacin administered at a dosage of 2 mg/kg would likely achieve the targeted CMAX-to-MIC50 and AUC-to-MIC50 ratios in the range of 5 to 42 and 33 to 268, respectively, which would minimize development of antimicrobial resistance by bacteria and maximize clinical and microbiologic cures. Although clinical studies are needed to confirm the therapeutic value of marbofloxacin, it is reasonable to assume that a minimal therapeutic orally administered dose of 2 mg/kg should be appropriate for control of most infections in chickens.

In our study, tissue depletion of marbofloxacin and its major metabolite N-desethyl-marbofloxacin after a 3-day dosing regimen was also determined. Marbofloxacin and N-desethyl-marbofloxacin concentrations in tissues obtained from the kidneys, liver, muscles, and skin plus fat were high initially and decreased over time. Seventy-two hours after administration of the last dose, we detected marbofloxacin and N-desethyl-marbofloxacin concentrations only in the liver (27.6 ± 0.9 and 98.7 ± 14.7 µg/kg, respectively) and kidneys (39.7 ± 4.2 and 69.1 ± 12.5 µg/kg, respectively). From a public health viewpoint, it is important to know about the persistence of a drug and its metabolites in edible tissues when it is administered for therapeutic purposes to food-producing animals. The next step is to define the withdrawal time necessary to ensure that any residues will decrease to concentrations less than an established MRL or tolerance level. Numerous experimental designs and statistical approaches have been used to establish the withdrawal time. The European Agency for the Evaluation of Medicinal Products recommends use of a linear regression technique as the method of choice.29 Using this approach, the withdrawal time is determined at the point at which the upper 95% tolerance limit for the residue is less than the MRL with 95% confidence. Maximum residue limits established by the European Union for marbofloxacin are 150 µg/kg for muscles, liver, and kidneys and 50 µg/kg for fat and skin in cattle and pigs, expressed as parent compound.25 In our study, taking into account MRL in cattle and pigs and considering marker residue to be the sum of parent drug and its metabolite, the withdrawal time could only be calculated for renal and hepatic tissues. The calculated withdrawal time was 5 days. Concentrations in the other tissues were too low (in regard to the MRL) to calculate a withdrawal time.

References

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