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Pharmacokinetic and residue studies of quinolone compounds and olaquindox in poultry

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(Pharmacokinetics of Veterinary Drugs, 11-12 October 1989, Fougeres, France)

Summary — Nalidixic acid and similar antimicrobial agents have been available for more than 20 years, mainly for treating infections caused by Gram-negative enterobacteria. Recently, several chemically related drugs, including oxolinic acid, pipemidic acid, piromidic acid and flumequine, have been developed. They are either naphthyridine-carboxylic acid or quinoline-carboxylic acid derivatives and, with nalidixic acid, are so-called quinolones. A major advance in antimicrobial chemotherapy was the synthesis of newer quinolones containing at least 1 fluorine atom and a piperazinyl group. These new fluoroquinolones have an extended antimicrobial spectrum compared to the first quinolone generation, and are highly active against most Gram-negative pathogens including the Enterobacteriaceae and Pseudomonas aeruginosa. The pharmacokinetic properties and residue levels of these quinolones and fluoroquinolones for which clinical experience or experimental information exists in poultry are reviewed here. On the other hand, administration of the quinoxaline-di-11-oxide, olaquindox, for medical purposes raises questions concerning the pharmacokinetic disposition of the drug and the risk of its residues in poultry. This paper presents information about the pharmacokinetic profile of olaquindox and the presence of its residues in chickens.

quinolone / poultry / pharmacokinetics / residues


quinolone / volaille / pharmacocinétique / résidus
INTRODUCTION

Among oral anti-bacterial agents, the quinolone class has been demonstrated to be effective in the treatment of Escherichia coli infections in poultry, especially colibacillosis in broilers. Nalidixic acid (a 1,8-naphthyridine derivative), the first agent in this series, and a number of other chemically related drugs (oxolinic acid, pipemidic acid, piromidic acid, flumequine), are active in vitro against a wide range of Gram-negative bacilli (with the exception of Pseudomonas aeruginosa) but inactive against Gram-positive organisms. In addition, the clinical use of first generation quinolones is often associated with the rapid emergence of resistant mutants (Fass, 1985). The development of new fluoroquinolones (norfloxacin, enoxacin, ciprofloxacin, ofloxacin, enrofloxacin, pefloxacin) with good systemic bioavailability and improved intrinsic antimicrobial activity especially against P aeruginosa and Gram-positive organisms, has renewed interest in this class of antimicrobial agents.

The primary target of nalidixic acid and oxolinic acid and probably all the other fluoroquinolones is DNA gyrase (topoisomerase II), an essential bacterial enzyme that maintains superhelical twists in DNA (Cozzarelli, 1980; Drlica, 1984; Gellert, 1981).

The theoretical advantage of fluoroquinolones led to the evaluation of their pharmacokinetic parameters in poultry and to assess their therapeutic potential and their residue levels in food-producing animals. The encouraging results obtained in the preliminary trials prompted us to review these agents. Other quinoxaline-di-N-oxide compounds, such as olaquindox, will also be discussed. The use of this drug in poultry for medical purpose (anti-bacterial activity) may or may not have a practical relevance.

STRUCTURE OF QUINOLONES

The general structures of two of the most studied classes of quinolones are shown in figure 1. Molecular modifications of the parent structures have been carried out in order to develop agents with higher potency and broader bacterial spectra. The results of structure-activity studies performed to date can be summarized as follows: maximum in vitro potency (expressed as MICs) and in vivo efficacy occur with a fluorine substituent at C-6 with the concomitant presence of an amino functionality of optimal size at C-7 (fig 2).

Fortunately, information on the dissociation, solubility and solubility-pH relationship for nalidixic acid, a model for the newer quinolones, is available in the literature (Grubb, 1979; Staroscik and Sulkowska, 1971; Sulkowska and Staroscik, 1975). Nalidixic acid has two pKₐ's which have been determined spectrophotometrically.

![Fig 1. General structures of quinolone antibacterial agents.](image-url)
(Staroscik and Sulkowska, 1971) by solubility measurements (Sulkowska and Staroscik, 1975) and by partition studies (Grubb, 1979). The spectrophotometric pK\(_a\) of 0.94 corresponds to the dissociation of a protonated heterocyclic nitrogen of nalidixic acid, while the spectrophotometric pK\(_{a2}\) value of 6.02 corresponds to the dissociation of the carboxylic acid group (Staroscik and Sulkowska, 1971). The dissociation scheme for nalidixic acid is given in figure 3. Their solubility–pH and partition–pH profiles have also been studied by Ogata et al (1984a) and Ismail and Gadalla (1983). The pK\(_a\)s determined by solubility were 1.03 ± 0.13 and 6.12 ± 0.03, whereas those determined by partition measurements were 0.86 ± 0.07 and 5.99 ± 0.03, respectively. In its neutral form (NH\(^0\)), between pH values of 2 and 5, nalidixic acid has a solubility of 8.3 x 10\(^{-6}\) M (19 µg/ml) (Staroscik and Sulkowska, 1971). Most of the new quinolones have dissociation constants for their carboxyl group which are very similar to that of nalidixic acid.

Fig 2. Basic structural modifications of quinolones that contribute to their antimicrobial activity. X = a variety of possible substitutions (from Neer, 1988).

Fig 3. The dissociation scheme of nalidixic acid.
dixic acid. Substitution at the 7-position appears to have little electronic or steric effect on the dissociation of the carboxyl group. In contrast to nalidixic acid, the new quinolone antimicrobials have a basic functional group in the 7-position which has a much higher pK_a than the heterocyclic nitrogen. This has a profound effect on their solubility and partitioning properties which in turn significantly influence their pharmacological and biopharmaceutical properties. The pK_a values of several quinolone antimicrobials have been determined (Ogata et al., 1984a, b). It appears that the pK_a corresponding to the carboxylic group is around 6.0 ± 0.3 and is relatively independent of substitution at the 7-position. On the other hand, the basic amine pK_a can vary between 5 and 9, depending upon the chemical nature of the side chain.

The structures of the six quinolones considered in the present report and the structure of olaquindox are given in figure 4.

PHARMACOKINETICS

The pharmacokinetic characteristics of 7 agents are shown in table I. After oral administration, these agents are more or less rapidly absorbed with peak plasma concentrations reached within 3 h. Piromidic acid, ciprofloxacin and olaquindox are the most rapidly absorbed, reaching a maximum level (T_max) after 0.19 – 0.22 h following administration. Norfloxacin is absorbed more slowly (T_max 0.30 h), but enrofloxacin, flumequine and oxolinic acid have the slowest rates of absorption with T_max of 1–2, 2 and 2.72 h, respectively. The peak plasma levels (C_max) reached are also different and dose-dependent. Single oral doses of each of the 7 drugs considered in the present review are able to reach peak

<table>
<thead>
<tr>
<th>Plasma parameters</th>
<th>OXO^a</th>
<th>PIRO^b</th>
<th>FLUM^c</th>
<th>NRO^d (mg/kg)</th>
<th>NOR^e</th>
<th>CIP^f</th>
<th>OLAQ^g</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>15 mg/kg</td>
<td>10 mg/kg</td>
<td>12 mg/kg</td>
<td>2.5</td>
<td>5</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>T_max (h)</td>
<td>2.72 (0.14)</td>
<td>0.19 (0.03)</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>0.30 (0.07)</td>
</tr>
<tr>
<td>C_max (μg/ml)</td>
<td>11.93 (0.29)</td>
<td>1.65 (0.09)</td>
<td>5</td>
<td>0.5</td>
<td>0.6</td>
<td>1.4</td>
<td>1.95 (0.16)</td>
</tr>
<tr>
<td>t_{1/2} β (h)</td>
<td>33.54 (3.88)</td>
<td>11.21 (0.77)</td>
<td>8</td>
<td>2–3.5 (0.4)</td>
<td>13.06 (1.18)</td>
<td>9.13 (0.30)</td>
<td>5.13 (0.19)</td>
</tr>
<tr>
<td>AUC (mg·h/l)</td>
<td>478.10 (33.10)</td>
<td>9.04 (0.74)</td>
<td>NA</td>
<td>NA</td>
<td>12.62 (0.69)</td>
<td>14.70 (1.36)</td>
<td>55.32 (2.28)</td>
</tr>
</tbody>
</table>

^a, b, e, f, g Anadón et al (unpublished data). Mean data from 8 experiments are presented, with the SEM between parentheses. 40 d old male broiler chickens (Hubbard x Hubbard) weighing 2.5 kg were used. Oxolinic acid, piromidic acid, norfloxacin, ciprofloxacin and olaquindox were administered orally, directly into the crop. The drug plasma concentrations were determined by HPLC as previously described (Groeneveld and Brouwers, 1986; Horii et al., 1987; Bates, 1979). Plasma levels were fitted to a 2-compartment open model. The half-life of the β phase (t_{1/2} β), the area under the concentration–time curve (AUC), the peak plasma level (C_max), and the time needed to reach C_max (T_max) were calculated (Wagner, 1976).

^c Chevalier et al (1982). Flumequine dissolved in gum arabic was administered orally to Warren hens. The flumequine concentrations in plasma were determined using a microbiological assay.

^d Seeher (1987). Eighteen 3–6 week old broiler chickens received enrofloxacin in drinking water. The enrofloxacin plasma concentrations were determined using a microbiological assay.

NA, data not available.
Pharmacokinetics of quinolone

Norfloxacin

Ciprofloxacin

Enrofloxacin

Plumequine

Piromidic acid

Oxolinic acid

Olaquindox

Fig 4. Structural formulae of quinolone and quinoxaline anti-bacterial drugs.
plasma levels above 1 μg/ml (and thus above the MIC for many organisms). The differences in C_max values among different agents probably reflect variability in gastrointestinal absorption. When given orally at an equivalent dose, ciprofloxacin produces higher values of C_max, and of the area under the curve (AUC) of the plasma level plotted versus time (AUC is related to bioavailability). The C_max of 3.54 μg/ml following the administration of 8 mg/kg of ciprofloxacin is higher than that observed for the same dose of norfloxacin (1.95 μg/ml). The drugs considered, with the exception of enrofloxacin, persisted in the body of chickens for a long time. The mean terminal plasma elimination half-life (t_1/2β) was 5.13 h for olaquindox, 8 h for flumequine, 9.13 h for ciprofloxacin, 11.21 h for piromidic acid, 13.06 h for norfloxacin and 33.54 for oxolinic acid. The mean t_1/2β of enrofloxacin is about 2–3.5 h.

The relatively long plasma elimination half-lives of norfloxacin and ciprofloxacin that we observed in chickens are not in agreement with values reported by Sheer (1987) for enrofloxacin. These differences may result from the use of different analytical methods (microbiological assay for enrofloxacin vs HPLC assay for norfloxacin and ciprofloxacin).

RESIDUE LEVELS

Few studies of tissue distribution and residue levels of quinolone and quinoxaline compounds in poultry have been reported. Table II summarizes the available results (Anadón et al, unpublished data). In poultry, the quinolone, oxolinic acid, piromidic acid and the quinoxaline compound, olaquindox, were widely distributed throughout the body with tissue concentrations exceeding 1 μg/ml 24 h after administration (table II). This good tissue penetration and high drug concentrations well above the

Table II. Tissue concentrations of oxolinic acid, piromidic acid and olaquindox after oral administration to chickens.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Tissue</th>
<th>Drug concentration (μg/g) on</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>day 1</td>
</tr>
<tr>
<td>Oxolinic acid</td>
<td>muscle</td>
<td>1.46 (0.15)</td>
</tr>
<tr>
<td>200 mg/kg</td>
<td>liver</td>
<td>2.16 (0.15)</td>
</tr>
<tr>
<td>single dose</td>
<td>kidney</td>
<td>2.38 (0.35)</td>
</tr>
<tr>
<td>Piromidic acid</td>
<td>muscle</td>
<td>1.03 (0.16)</td>
</tr>
<tr>
<td>10 mg/kg/d</td>
<td>liver</td>
<td>1.19 (0.10)</td>
</tr>
<tr>
<td>for 3 d</td>
<td>kidney</td>
<td>2.06 (0.28)</td>
</tr>
<tr>
<td>Olaquindox</td>
<td>muscle</td>
<td>3.33 (0.84)</td>
</tr>
<tr>
<td>20 mg/kg/d</td>
<td>liver</td>
<td>3.69 (0.50)</td>
</tr>
<tr>
<td>for 3 d</td>
<td>kidney</td>
<td>1.43 (0.23)</td>
</tr>
</tbody>
</table>

Values are presented as means (μg/g of tissue) from 6 chickens with the SEM between parentheses. ND = not detected. 40 d old male broiler chickens (Hubbard x Hubbard) weighing 2.5 kg were used. Oxolinic acid, piromidic acid or olaquindox was administered orally, directly into the crop. The drug concentrations in tissues were determined by HPLC as previously described (Groeneveld and Brouwers, 1986; Horii et al, 1987; Bories, 1979).
MIC for most bacterial pathogens (Barry, 1989) suggest the potential clinical use to treat bacterial infections in poultry. In most species of Enterobacteriaceae, nalidixic acid and pipemidic acid have similar activities (median MICs of 1.0–4.0 μg/ml); pipemidic acid is less active against Gram-negative bacteria (median MICs of 1.0–10 μg/ml). The first compound in the quinolone series (oxolinic acid) is much more active; the median MICs for different species are ≤0.5 μg/ml. Norfloxacin is 10–100 times more active than nalidixic acid. Other fluoroquinolones are also extremely active against the enteric bacilli; ciprofloxacin is the most potent quinolone reported (Barry, 1989). Among various quinoxaline-1,4-dioxide derivatives synthesized to date, the growth promoter olaquindox is also used in the treatment and prevention of infectious diseases caused by diverse bacteria, such as Salmonella and E coli (Bertschinger, 1976) (median MICs of 8–16 μg/ml).

However, on the basis of detected residue levels, specific requirements might include a preslaughter withdrawal time. Assays of drug concentrations in muscle, liver and kidney showed that oxolinic acid, pipemidic acid and olaquindox persisted for a long time in the body of chickens. Olaquindox was found to be the slowest drug eliminated from the body with an unchanged drug concentration of 0.03, 0.11 and 0.12 μg/g of muscle, liver and kidney tissues, respectively, 14 d after oral drug administration.

No data have yet been published on the tissue penetration of new fluoroquinolones (norfloxacin, ciprofloxacin, ofloxacin, enoxacin and pefloxacin) in poultry. However, taking into account data obtained in other animal species and in man (Gilfillan et al, 1984; Hooper and Wolfson, 1985; Walker et al, 1989), they are also likely to have good tissue penetration. A study on the physiological disposition of enrofloxacin has been reported (Sheer, 1987). After a single oral dose of 10 mg/kg to chickens, enrofloxacin was rapidly and widely distributed to tissues. Concentrations above 1 μg/g were found 4–6 h after drug administration in lung, heart, liver, spleen, kidney and muscle. However, the drug was also eliminated quickly from tissues. Twenty-four hours after drug administration, the residue levels of enrofloxacin fell below 0.02–0.05 μg/g of tissue. This indicates that the duration of the antimicrobial effect is shorter, since it depends upon the time during which the free drug concentration exceeds the MIC of susceptible pathogens (Baggot, 1980).

CONCLUSIONS

The common pharmacokinetic properties of the quinolones are: 1) a rapid oral absorption, 2) attainable serum and tissue concentrations above the MIC for most Gram-negative and many Gram-positive organisms, and 3) relatively long half-lives in plasma, allowing dose intervals of at least 12 h. These features suggest possible clinical applications.

Although many investigations remain to be done, since olaquindox persists in the body of chickens for at least 14 d, this drug may pose a toxicological risk for man if a preslaughter withdrawal time is not observed. Currently, available data on oxolinic acid and pipemidic acid residues recommend a preslaughter withdrawal time of 8 d.

ACKNOWLEDGMENTS

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