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Comparative pharmacokinetics study of fluoroquinolones in broiler chickens

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ABSTRACT

The serum concentrations and pharmacokinetics of levofloxacin and danofloxacin in broiler chickens was compared following single intravenous (IV) or oral administration at 10 mg/kg of body weight (b.w.). Serum concentrations of levofloxacin and danofloxacin were determined by specific and sensitive high performance liquid chromatography (HPLC) methods. Pharmacokinetic parameter values for both fluoroquinolones were calculated by non-compartmental analysis. Following IV administration, the elimination half-life ($T_{1/2ß}$) was two-fold higher and the mean residence time (MRT) was three-fold higher for danofloxacin compared to levofloxacin. The values for total body clearance (Cl_B) were 13.67 vs. 64.10 ml/min.kg and volume of distribution at steady state (V_{dss}) were 6.84 vs. 2.47 L/kg. However, area under the serum concentration vs. time curve of levofloxacin was greater than for danofloxacin. Maximum plasma concentration (C_{max}) after oral administration was 1.41 and 0.706 µg/ml for levofloxacin and danofloxacin, attaining at one and two hours for both drugs, respectively. Systemic bioavailability (F) was 89% for levofloxacin and < 100% for danofloxacin. Furthermore, the apparent volume of distribution (V/F) of danofloxacin was (37.92 L/kg) significantly higher than that of levofloxacin (15.40 L/kg). Following oral administration, the C_{max}/MIC ratio of 14.11 and 7.10 and AUC/MIC ratio of 108.68 and 58.50 for levofloxacin and danofloxacin, respectively, indicates potential clinical and bacteriological efficacy of levofloxacin. Based on these parameters, a dose of 10 mg/kg b.w. of levofloxacin given orally every 24 h in chickens can maintain effective serum concentrations with bacterial infections with MIC_{90}> 0.1 µg/ml.

Keyword : IV :intravenous, b.w : body weight , HPLC : high performance liquid chromatography
$T_{1/2ß}$: elimination half-life, MRT : mean residence time

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INTRODUCTION

In veterinary clinical practice the sensitivity of a given animal species to a certain drug can be attributed to pharmacodynamic and pharmacokinetic variations. In contrast to human medicine where individual differences are of primary importance, inter-species and also inter-breed distinctions are crucial in comparative veterinary medicine **(Jerzsele, 2012)**. Increasing worry has been expressed about the extensive use of fluoroquinolones in poultry, as resistant zoonotic organisms may transmit to human. A relationship has been reported between septicaemic human and animal pathogenic bacterial strains **(Johnson *et al.*, 2002)**, confirming the demand for appropriate use of these compounds. The ability to attain clinical efficacy and to minimize the spread of resistant pathogens is a correlation between the pharmacokinetic and pharmacodynamic behaviors of fluoroquinolones **(Wise, 2003)**. Levofloxacin and danofloxacin belong to the group of synthetic fluoroquinolone compounds developed mainly for veterinary use **(Garcia *et al.*, 2000)**. They act predominantly by inhibiting the enzyme topoisomerase II, hence suppressing DNA and RNA replication. Fluoroquinolones result in concentration-dependent killing of many Gram-negative microorganisms **(Aliabadi and Lees, 2001; Sarasola *et al.*, 2002)** as well as atypical pathogens such as *Mycoplasma* and *Chlamydia* **(Eliopoulos *et al.*, 1996)**. Fluoroquinolones show rapid and extensive tissue distribution in interstitial fluid, skin and bones are 35-100% of those obtained in serum, where as bronchial secretions and prostatic concentrations are two to three times of corresponding serum concentrations **(Jerzsele, 2012)**. Penetration into CSF

(cerebrospinal fluid) is approximately 25% of serum concentration **(Davis *et al.*, 2006)**. Fluoroquinones attain high intracellular concentrations in macrophages and neutrophils. Intracellular concentrations are 4-10 times greater than plasma concentrations. The pharmacokinetics of levofloxacin and danofloxacin has been investigated in avian species including pheasants, guinea fowls and Japanese quails **(Dimitrova *et al.*, 2014)**, turkeys **(Haritova *et al.*, 2006)**, ducks **(Aboubakr and Soliman, 2014)**, chickens **(Knoll *et al.*, 1999; El-Gendi *et al.*, 2001, Deng *et al.*, 2003)**. However, there is little information concerning comparative clinical study to recommend the most efficacious fluoroquinones in poultry industry. Consequently, the aim of this investigation was:

- To compare serum concentrations of levofloxacin and danofloxacin in broiler chickens following single intravenous or oral administration at 10 mg/kg body weight using high performance liquid chromatography (HPLC) assay
- To determine and compare pharmacokinetics parameters of levofloxacin and danofloxacin using non compartmental and compartmental analysis models to recommend the most appropriate antibacterial one in broiler chickens.

REVIEW OF LITERATURE

In the present work the pharmacokinetics of levofloxacin and danofloxacin as two drugs commonly used in veterinary practice, were studied in chickens. In this respect, the following literature revealed the kinetic aspects of the tested antibiotics in different species were also reported.

1-Levofloxacin:-

1-Antibacterial activity:

Fu *et al*. (1992) compared the antibacterial activity of levofloxacin, ofloxacin and ciprofloxacin and with other antibiotics. They found that levofloxacin was equally active or up to 4 fold more active than ofloxacin against all 801 organisms tested. Levofloxacin was 2-fold more active than ciprofloxacin against *Streptococcus pneumoniae* and two to four-fold more active than ciprofloxacin against *Staphylococcus aureus*, *Xanthomonas maltophilia*, and *Bacteroides fragilis*, most members of the family Enterobacteriaceae, such as *Escherichia coli*; *Klebsiella pneumoniae*; Citrobacter, Proteus, Salmonella, and Yersinia spp.; and *Pseudomonas aeruginosa*. Moreover, levofloxacin was 2-8 folds more active than ciprofloxacin against coagulase-negative *staphylococci* and *Acinetobacter spp*. and inhibited 90% of *streptococci* at concentrations of 1 to 2 µg /ml. The *in vitro* DNA gyrase inhibitory activity of levofloxacin was as potent as that of ciprofloxacin, with a 50% inhibitory concentration of 0.65 µg/ml against an *E. coli* enzyme. *In vivo*, oral treatment with levofloxacin was as efficacious as or more efficacious than that with ciprofloxacin in

systemic as well as pyelonephritis infections in mice. Levofloxacin achieved higher concentrations in the serum and tissue of mice than did ciprofloxacin.

Lafredo *et al*. (1993) studied the resistance of *Streptococcus pneumoniae* to quinolones *in vitro*, twelve strains of *Streptococcus pneumoniae* were serially exposed to increasing concentrations of levofloxacin, temafloxacin, ciprofloxacin and norfloxacin for five passages. Wild-type and passaged strains were tested for susceptibility to quinolones, macrolide and penicillin G. They found a 2-fold increase for levofloxacin but a 32-fold increase for ciprofloxacin, a 16-fold increase for temafloxacin and an 8-fold increase for norfloxacin at MIC_{90} (minimum inhibitory concentration of the drug that kill 90% of microbes). Among 16 ciprofloxacin-induced resistant strains, 14 were susceptible to levofloxacin.

Yamane *et al*. (1994) compared levofloxacin, the S-(-)-isomer of ofloxacin, to ofloxacin and ciprofloxacin against > 6000 recent clinical isolates of Gram-positive and Gram-negative bacteria from six different countries. This study demonstrated a high level of antibacterial activity of levofloxacin against all the members of *Enterobacteriaceae* [minimum inhibitory concentration that kill 50% of microbes (MIC_{50s}), < or = 0.03 to 0.12 mg/L] except *Providencia rettgeri* (MIC_{50}, 2 mg/L), and *Providencia stuartii* (MIC_{50}, 1 mg/L).Oxacillin-susceptible *staphylococci* (MIC_{50s}, 0.12 to 0.25 mg/L), *enterococci* (MIC_{50s}, 0.5 to 2 mg/L), and *streptococci* (MIC50s,

0.5 mg/L) were also susceptible to levofloxacin. Levofloxacin was also active against non-enteric Gram-negative bacilli, including *Acinetobacter species* (MIC_{50s}, < or = 0.03 to 1 mg/L), *Pseudomonas species* (MIC_{50s}, 0.5 to 1 mg/L) and *Xanthomonas maltophilia* (MIC_{50}, 0.5 mg/L).levofloxacin inhibited 50% and 90% of all the tested strains at the concentrations of 0.12 and 4 mg/L, respectively. The activity of levofloxacin was generally two-fold greater than ofloxacin and equal to or slightly less potent than ciprofloxacin.

Edelstein *et al*. (1996) studied the *in-vitro* activity of levofloxacin against clinical isolates of *Legionella spp* in guinea pigs, and use in experimental *Legionella pneumophila* pneumonia. They determined the activities of levofloxacin and ofloxacin against 22 clinical *legionella* isolates by micro broth dilution susceptibility testing. They found that the drug concentrations required to inhibit 90% of strains tested was 0.032 mg/L for levofloxacin. Levofloxacin (0.25 mg/L) reduced bacterial counts of two *L. pneumophila* strains grown in guinea pig alveolar macrophages by 1 log10, but re-growth occurred over a 3 day period; levofloxacin (1 mg/L) reduced bacterial counts by 2-3 log10 cfu/mL (colony forming unit/milliliter) Levofloxacin was significantly more active than erythromycin, and as active as ofloxacin or ciprofloxacin in this assay. Levofloxacin is effective against *L. pneumophilain in-vitro* and in a guinea pig model of legionnaire's disease.

Cormican and Jones (1997) compared compound LB20304 (a novel pyrrolidine substituent fluoronaphthyridone carboxylic acid) with ciprofloxacin, levofloxacin, ofloxacin, and trovafloxacin against over 800 pathogens, most from blood stream infections. They found that LB20304 was the most active agent against gram-positive species including strains observed to be resistant to other fluoroquinolones and glycopeptides. The potency of LB20304 (MIC_{50}, 0.03 µg/ml) against the Enterobacteriaceae was exceeded only by that of ciprofloxacin (0.015 µg/ml). It has limited activity against gram-negative anaerobes.

North *et al*. (1998) stated that the bactericidal effect of levofloxacin was shown in strains of *Escherichia coli*, *Pseudomonas aeurginosa*, and *S. aureus* in that the measured MIC (minimum inhibitory concentration) was identical to the measured minimum bactericidal concentration (MBC).Levofloxacin act by inhibiting bacterial DNA gyrase, an essential type II topoisomerase, and the enzyme which catalyze supercoiling, relaxing, knotting and catenating. Levofloxacin has an antibacterial effect against gram-Gram negative (*Escherichia coli*, *Haemophilus influenzae*, *Klebsiella pneumoniae, Enterobacter sp*., *Salmonella sp*., *Shiglla sp*., *Campylobacter sp*. ,*Neisseria gonorrhoeae*, *Moraxella catarrhalis*, *Proteus mirabilis*, and *Pseudomonas aeruginosa*), Gram positive (*methicillin-sensitive Staphylococcus aureus, Streptococcus pneumoniae*, *Enterococcus faecalis*, *Corynebacterium jeikeium*, *Listeria monocytogenes*, *Mycobacterium tuberculosis*and *Streptococcus pyogenes*),

and atypical bacterial pathogens (*Chlamydophila pneumoniae* and *Mycoplasma pneumoniae*).

Blondeau (1999) compared the *in-vitro* antimicrobial activities of respiratory quinolones and they found that levofloxacin has activity against gram positive bacteria with MIC_{90} of 0.5-2 mg/L for *E. Faecalis*, 2-32 mg/L for *E. faecium*, 0.25 for *MSSA (methicillin susceptible staphylococcus aureus)*, 16 mg/L for *MRSA (Methicillin resistant Staphylococcus aureus)*, 0.5-1 mg/L for *S. epidermidis*, 1-2 mg/L for *S. pneumoniae* and 1 mg/L for *S. pyogenes*. And also has activity against gram negative bacteria with MIC_{90} of 0.06-<0.5 mg/L for *Escherichia coli* and *Enterobacter spp*., 0.03-0.47 mg/L for positive B-*lactamase H. influenzae*, 0.03-0.32 mg/L for negative *B-lactamase H. influenzae*, 0.12-0.25 mg/L for *Klebsiella pneumoniae*, <0.015-0.25 mg/L for *Klebsiella spp*., 0.06-0.094 mg/L for positive *B-lactamase M. catarrhalis*, 0.06 mg/L for negative *B-lactamase M. catarrhalis*, 2 mg/L for *Morganella morganii*, 0.008 mg/L for *Neisseria spp*., 0.03-<0.5 mg/L for *Proteus spp*., 0.5->4 mg/L for *P. aeruginosa*, 4 mg/L for *Stenotrophomonas maltophilia*, 2 mg/L for *Serratia spp*., <0.015 mg/L for *Citrobacter spp*.. Also have activity against atypical pathogens with MIC_{90} of 0.25-0.05 mg/L for *Chlamydia pneumoniae*, 0.25-0.5 mg/L for *Chlamydia trachomatis*, 0.03 mg/L for all *Legionella spp*.