بسم الله الرحمن الرحيم

MONA MAGHRABY

شبكة المعلومات الجامعية

التوثيق الالكتروني والميكروفيلم

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جامعة عين شمس

التوثيق الإلكتروني والميكروفيلم

قسم

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Effect of probiotics on some pharmacokinetic aspects of difloxacin

A *Thesis Submitted By*

Hend Fouad Mohamed El Stuhy

(Master degree)

(Cairo University., 2016)

To

Cairo University

Faculty of Veterinary Medicine

For The PhD Degree in Veterinary Medical Sciences

(Pharmacology)

Under Supervision of

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Supervision sheet

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ABSTRACT

The influence of probiotics on the pharmacokinetics and tissue residue of difloxacin in apparently healthy and *Mycoplasma gallisepticum* infected chickens was studied after intravenous and oral administrations at a dose of 10 mg/kg.b.wt. The chickens were classified into two main groups each one subdivided into 6 subgroups: the first one was used for studying the impact of probiotics on the pharmacokinetic features and tissue residues of difloxacin in healthy chickens. The 6 subgroups are allocated into 4 subgroups for studying the effect of probiotics on the pharmacokinetics of difloxacin in healthy chickens (2 with and 2 without probiotic treatment). The other two subgroups were used for studying the effect of probiotic on difloxacin tissue residues. The second group was used for studying the impact of probiotics on the pharmacokinetic features and residues levels of difloxacin in *Mycoplasma gallisepticum*-experimentally infected chickens in which the 6 subgroups were allocated into 4 subgroups(2 with and 2 without probiotic treatment) for studying the effect of probiotic on the pharmacokinetic of difloxacin in MG infected chickens. The other two subgroups were used to study the effect of probiotic on difloxacin tissue residues. Probiotic was given from day 5 after hatching to day 21 of age and difloxacin was given after overnight fasting of the last probiotic dose either IV or oral in a single dose of 10 mg/kg. Difloxacin residues were estimated after 5 consecutive days of oral administration and the edible organs (muscle, liver, kidney and gizzard) were collected from slaughtered birds 1, 3, 5 and 7 days after the last dose.

Plasma concentrations and tissue residues of difloxacin were estimated by using HPLC technique. The plasma difloxacin concentrations-time course was best fitted to a 2 compartment open model. Following intravenous administration, plasma concentration of difloxacin at zero time was significantly higher (12.09±0.07 *vs* 11.82±0.1h) in probiotic-pretreated chickens as compared to non-treated birds and a significantly prolonged half-life (4.09±0.03 vs 3.75±0.02 h) in probiotic-pretreated chickens as compared to non-treated birds . The volume of distribution and the clearance rate although achieved higher values, however, the significant difference did not occur. The areas under curves (AUC_{0-t}, AUC_{0-inf}, AUMC) and the MRT were much higher in probiotic-pretreated chickens. The–elimination half-life ($t_{½\beta}$) of difloxacin in MG-infected chickens (4.55±0.05 h) was significantly shorter than probiotic treated MG-infected birds (4.75±0.09 h) and the volume of distribution at steady state (v_{ss}) was larger in the infected chickens as compared to probiotics-pretreated MG-infected one (4.16±0.07 and 4.05±0.07 mg/(µg/ml, respectively). Following oral administration, the drug reached its peak plasma concentrations (C_{max}) of 1.8 ± 0.19 µg/ml at maximum time (t_{max}) of 2.66 ± 0.06 h in probiotic non treated normal chickens, while in probiotic-pretreated healthy chickens, the C_{max} 2.31± 0.17 µg/ml attained at t_{max} of 2.5 ± 0.03h. In the infected group, the MRT was significantly shorter in infected chickens pretreated with probiotics (5.36±0.03 h) as compared with non-treated one (5.71±0.09 h $P<0.05$). After repeated oral administration of difloxacin at a dose of 10 mg /kg.b.wt once daily for 5 successive days, difloxacin was detected in all edible tissues up to the 3rd day and in the liver and kidney for 5 days after the last day of administration. The liver and kidney contained the highest concentrations of difloxacin. The residues of difloxacin 24 hours after the last oral dose was lower than the recommended MRLs. In conclusion, the pharmacokinetic parameters of difloxacin were altered due to concurrent administration of probiotics and the withdrawal period of difloxacin may be re-evaluated when concurrently administered with probiotics.

Key words: probiotics, pharmacokinetics, difloxacin, *Mycoplasma gallisepticum*, HPLC.

ACKNOWLEDGMENT

Firstly, I express my sincere gratitude to ***gracious ALLAH*** *who gave me the ability and patience to finish this work.*

I am greatly Indebted to ***Prof.Dr.Mohamed Atef Shehata*** *Professor of Pharmacology, Faculty of Veterinary Medicine, Cairo University for his supervision through this work, planning the work, his moral support, valuable advices, fruitful discussion and encouragement during the entire course of thiswork.*

My sincere gratitude and deepest thanks to ***Prof. Dr. Attia Hassan Atta****, Professor of Pharmacology, Faculty of Veterinary Medicine, Cairo University for his supervision through this work, planning the work, fruitful discussion, facilities, helpful guidance and continuous encouragement during performance of this work.*

I would like to express my great, cardial and sincere thanks and deep appreciations to ***Prof.Dr.Ashraf Shehata Darwish****, Senior Researcher of pharmacology ,Animal Health Research Institute, Dokki to for his supervision, continual encouragement, fruitful advices, kind supervision and valuable help.*

Finally, I would like to express my deep thanks to all members of Pharmacology Department, Faculty of Veterinary Medicine, Cairo University and to every hand helped me to complete this work.

Dedicated to

My parents

My husband

My sister

My brother

My daughter

My son

Who

Shared the responsibility of bringing me up to be grateful

and

To all those who taught me

CONTENTS

The Pharmacokinetic Abbreviations

Symbol	Definition
A	Zero-time intercept of the distribution slope.
B	Zero time intercept of elimination slope .
A	The distribution rate constant
B	Elimination rate constant.
AUC_{0-t}	Area under the curve.
AUC_{0-inf}	Total area under the concentration–time curve from zero to infinity.
AUMC	Area under the first moment curve.
C^0	The drug concentration in the serum at zero time immediately after a single intravenous injection .
C_{max}	Maximum serum concentration of drug in blood after extravascular administration .
Cl	Total body clearance.
Cl_2	Inter-compartmental clearances.
CL/F	The body clearance corrected for bioavailability after non-intravenous administration.
F %	Bioavailability, is the fraction of an administered drug that reaches the systemic circulation.
K_{ab}	First - order absorption rate constant (h^{-1}).

K_{12} Rate constant for passage from central to peripheral compartment.

K_{21} Rate constant for passage from peripheral to central compartment.

K_{10} First-order elimination rate constant from central compartment.

MRT Mean residence time

$t_{1/2\alpha}$ Distribution half - life .

$t_{1/2\beta}$ Elimination half - life .

T_{max} The time to maximum drug plasma concentration

V Apparent volume of central compartment.

V_2 Apparent volume of peripheral compartment.

V_{ss} Volume of distribution at steady state.

V/F The volume of central compartment corrected for bioavailability after non-intravenous administration.

Chapter 1

INTRODUCTION

Antimicrobials are currently used for curing of bacterial diseases in poultry manufacture. The improper use of antibiotics develops bacterial resistance to antimicrobial agents in poultry farms. Therefore, alternatives of antibiotics such as probiotics, oligosaccharides, herbal drugs, and essential oils are given as feed additives in poultry feeding (Pavlova *et al*, 2015).

Streptococcus spp., Lactobacillus spp., Bifidobacterium, and Bacillus spp. are offered as feed additives to broilers to improve weight gain, feed conversion ratio, and consequently decrease death rates (Griggs and Jacobs, 2005; Kabir, 2009; Santini *et al.*, 2010). Many data have been published about the role of the intestinal microflora in the digestion, nourishment, uptake, and defence mechanisms in the body. Therefore, there is an interest in the the effect of alteration of its composition on its activity by supplementing probiotics since probiotics can modify the activity of intestinal microflora.

The intestinal microflora is now accepted to play an important role on the disposition of many compounds, since orally administered probiotics can change intestinal microflora composition and enzyme activities (Stojančević *et al.*, 2013).

Mycoplasma gallisepticum infections can cause major economic losses in poultry farms due to reduced feed efficiency, decreased growth rate, decreased egg production, induced chronic respiratory disease and downgraded carcasses of birds sent to slaughter (Gharaibeh and Al Roussan, 2008). *M. gallisepticum* infections are among the notifiable diseases to the World Organization for Animal Health (OIE). Although, Mycoplasma has been eradicated from most commercial chicken and turkey farms in the United States; it remains endemic in many other countries.