جامعة القاهرة
كلية الطب البيطري
قسم الأدوية

تأثير الكركم على الحركية الدوائية للماربوفلوكساسين فى الدجاج اللاحم

رسالة مقدمة من

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ABSTRACT

This investigation was carried out to elucidate the influence of turmeric pre-treatment on the pharmacokinetic of marbofloxacin following single oral and intravenous administration in broiler chickens. Chickens were divided into four groups of seven each. Group-I and II were administered marbofloxacin (5 mg/kg body weight {b.w.}) intravenously and orally, while animals in group-III and IV received similar dose of marbofloxacin (5 mg/kg b.w.) intravenously and orally, after oral pre-treatment with turmeric (100 mg/kg b. w. per day, 10 days). Blood samples were collected from the right wing vein at 0 (blank sample), 0.166, 0.25, 0.33, 0.5, 0.75, 1, 2, 4, 6, 8, 10, 12, 18, 24 and 48 hr in all groups. The Serum concentrations of marbofloxacin were determined by a reverse phase high-performance liquid chromatography (HPLC) with UV detection at 295 nm. The serum concentrations were significantly higher in turmeric treated chickens following oral and intravenous routes. The pharmacokinetic data revealed that turmeric treated chickens had significantly higher area under curve (AUC), volume of distribution (V_c) and mean residential time (MRT). After oral dosing the absorption rate constant (k_{ab}) is significantly higher than the elimination rate constant (k_{el}). This could result in the presence of *in vivo* flip-flop pharmacokinetics. The delayed absorption was evident following oral administration, which limited the elimination and demonstrated sustained release from entero-hepatic circulation Turmeric ameliorates the systemic and relative bioavailabilities of marbofloxacin after oral administrations in broiler chickens.

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المستخلص

تم دراسه تأثير الكركم على المسار الحركى للماربوفلوكساسين بعد تجريعه عن طريق الفم و الحقن الوريدى في الدجاج اللاحم. تم تقسيم الدجاج إلى أربع مجموعات من سبعة لكل منهما. المجموعة الأولى والثانية ماربوفلوكساسين (5 ملجم / كجم من وزن الجسم عن طريق الوريد و عن طريق الفم، في حين أن الطيور في المجموعة الثالثة والرابعة تلقت جرعة مماثلة من الماربوفلوكساسين (5 ملجم / كجم من وزن الجسم) عن طريق الوريد و عن طريق الفم بعد تجريع الكركم (100 ملغ / كجم من وزن الجسم يوميا لمدة 10 يوما). جمعت عينات الدم من الوريد اليميني عند 0 و 0.166 و 0.25 و 0.33 و 0.5 و 1 و 2 و 4 و 6 و 8 و 10 و 12 و 18 و 24 و 48 ساعة في جميع المجموعات. تم تحديد تركيزات المصل من الماربوفلوكساسين بواسطة كروماتوجرافيا سائل عالي الأداء عند 295 نانومتر. وكانت تركيزات مصل الدم للماربوفلوكساسين أعلى بكثير في الدجاج المجرع بالكركم عن طريق الفم وعن طريق الوريد. وكشفت الحركية الدوائية للماربوفلوكساسين أن الدجاج المجرع بالكركم كانت قيمه المساحة تحت المنحنى وحجم التوزيع الظاهرى ومعدل الامتصاص بعد الجرعات عن طريق الفم أعلى بكثيرمن الطيور التى لم تجرع بالكركم. ويمكن تفسير الامتصاص المتأخر للماربوفلوكساسين بعد تناوله عن طريق الفم نتيجة تأخير افرازه عن طريق العصارة الصفراوية فى الكبد، و تأكد الدراسه على أن الكركم يزيد من الاستفادة الحيوية للماربوفلوكساسين عن طريق الفم في الدجاج اللاحم.

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Effect of turmeric on the pharmacokinetics of marbofloxacin in broiler chickens

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For

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CONTENTS

INTRODUCTION

Enhanceing the bioavailability of poorly absorbed antibacterial molecules has always been a vital aspect of drug development plans, as it reduces the drug dosage and frequency resulting in reduced toxicity and bacterial resistance **(Dudhatra *et al*., 2012)**. Marbofloxacin is a fluoroquinolone member developed solely for animals. It has an additional oxadiazine ring, which may delay the elimination pattern and indeed increases its bioavailability after extravascular routes, **(Heinen, 2002)**. Marbofloxacin exhibits high bactericidal activity against a broad spectrum of aerobic Gram-negative and some Gram-positive bacteria, and against Mycoplasma spp. **(Drugeon *et al*., 1997)**.

The pharmacokinetics of marbofloxacin has been extensively investigated in rabbits **(Abo-El-Sooud and Goudah, 2010)**; turkeys (**Haritova *et al*., 2006)**; ostriches **(De Lucas *et al*., 2005)**; Muscovy ducks **(Yuan *et al*., 2011)** and broiler chickens **(Ding *et al*., 2013)**. Orally administered marbofloxacin is not as commonly used in poultry as other fluoroquinolones, because of its lower bioavailability after gastrointestinal absorption **(Anadon *et al*., 2002)**. **Zhang *et al*., 2011** found that marbofloxacin and other fluoroquinolones inhibit the enzyme activity, protein levels and mRNA expression of liver cytochrome P450

(CYP) 1A and 3A in male broiler chicks raising the possibility of drug–drug interaction when using these compounds.

Bioenhancers are chemical units that augment the bioavailability of the drugs when are given concurrently and they do not exhibit synergistic effect with the drug. The need for bioenhancers arises due to drugs, which are poorly available and administered for long periods **(Tatiraju *et al*., 2013)**.

Although most of the bioenhancers possess several pharmacological activities at different concentrations, to be considered as a novel

Curcuma longa or turmeric is a tropical plant native to southern and southeastern tropical Asia. A perennial herb belonging to the ginger family, turmeric measures up to 1 m high with a short stem and tufted leaves. The most active component in turmeric is curcumin, which may make up 2 to 5% of the total spice in turmeric especially in cheap supplements on the markets (**Aggarwal *et al*., 2005)**. Curcumin is a diferuloylmethane present in extracts of the plant. Curcuminoids are responsible for the yellow color of turmeric and curry powder **(Lal, 2012)**. Curcumin is a common food flavor item used as ethno-therapy for a variety of diseases. It is a flavonoid in nature had the ability to suppress drug metabolizing enzymes especially CYP3A4 in liver and is also capable of inducing change in drug transporter P-glycoprotein (P-gp) and thus

increased the absolute bioavailability of concomitant drugs via increasing the maximum absorption concentration (C_{max}) and area under the serum concentration-time curve (AUC) **(Zhang *et al*., 2007)**. Moreover, **Basu (2004)** found that curcumin suppresses UDP-glucuronyl transferase level in intestine and hepatic tissues. It also modifies the physiological activity in the gastrointestinal tract leading to better absorption of drugs.

The aim of the present study was to evaluate the effect of turmeric pre-treatment on the gastrointestinal absorption patterns and bioavailability of marbofloxacin after oral administration in broiler chickens.

REVIEW OF LITERATURE

Marbofloxacin

Petracca *et al* (1993) investigated influence of pregnancy and lactation on pharmacokinetics of marbofloxacin in sows. Six pregnant sows were treated in early pregnancy, late pregnancy and during lactation. Marbofloxacin was administered (2 mg/kg body weight) intravenously and orally. The active drug concentration in the plasma was quantitated by use of HPLC. Pharmacokinetic parameters were calculated by use of statistical moments. In lactating animals, the concentrations in milk were also determined by HPLC. Mean elimination half-life of the drug after oral administration was significantly shorter in lactating sows (5.74 h) than that of the early pregnancy group (10.09 h). Total body clearance was highest in the lactating sows (3.27 ml/min.kg body weight). The volume of distribution was large in all physiological states studied indicating good tissue penetration. Bioavailability was about 80% in pregnant and lactating sows. Antimicrobial secretion in milk contributed greatly to marbofloxacin elimination. These results indicate an important influence of lactation on marbofloxacin pharmacokinetics in sows. Therefore, in such cases, marbofloxacin dose should be increased during lactation.

Wolfson and Hooper (1985) found that marbofloxacin acts by inhibition of bacterial DNA-gyrase and has high antimicrobial activity *in vitro* against a wide range of gram-negative and some gram-positive bacteria (*Staphylococcus aureus, Staphylococcus intermedius, Escherichia coli, Klebsiella sp., Pasteurella multocida, Pasteurella haemolytica* and *Haemophilus somnus* and Mycoplasma. Other microorganisms which marbofloxacin is effective against are Aeromonas, Brucella, *Chlamydia trachomatis*, Enterobacter, Proteus, *Pseudomonas aeruginosa*, Salmonella, Serratia, Shigella, Staphylococci (including penicillinase-producing and methicillin-resistant strains), Vibrio, Yersinia.

Schneider *et al* (1996) investigated the pharmacokinetics of marbofloxacin in dogs after oral and parenteral administration. Six dogs were treated with a single intravenous (i.v.) dose (2 mg/kg) of marbofloxacin, followed by single oral (p.o.) doses of marbofloxacin at 1, 2 and 4 mg/kg, according to a three-way crossover design. The same experimental design was used for the subcutaneous (s.c.) route. In addition, a long-term trial involving eight dogs given oral doses of marbofloxacin at 2, 4 and 6 mg/kg/day for thirteen weeks was carried out. Plasma and urine samples were collected during