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PHARMACOKINETIC STUDIES ON TULATHROMYCIN IN CONTROLLING RESPIRATORY DISEASES IN HEALTHY AND FEBRILE FEEDLOT CALVES

(With 2 Tables and One Figure)

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دراسات فارماكوكينيتيكية على التلاثرومايسين في عجول التسمين السليمة والمحمومة

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أجريت هذه الدراسة على المسار الحركي لعقار التلاثرومايسين في عجول التسمين السليمة والمحمومة ، حيث تم حقن جرعة واحدة من العقار تحت الجلد ٢,٥ مليجرام/كجم في عدد ١٠ من العجول (عدد ٥ سليمة وعدد ٥ محمومة) تتراوح أعمارها من ٤-٦ أشهر وتم جمع عينات من مصل الدم لقياس مستوى الدواء بها. أظهرت النتائج أن امتصاص التلاثرومايسين كان سريع ومكثف ووصل لأعلى مستوى في مصل الدم خلال ساعتين بعد الحقن ، حيث كان أعلى تركيز في السيرم ٠,٦٥ و ٠,٥٩ ميكروجرام/مل بعد ٢ و٢ساعة وفترة نصف العمر ٢٥,١٧ و ٢٤,١٤ساعة للعقار في العجول المحمومة والسليمة على التوالي. كما أظهرت النتائج أن تركيز التلاثرومايسين يظل في مصل الدم مساو أو أعلي من أقل تركيز مثبط لـ ٩٠% من الميكروبات الرئيسية المسببة للأمراض التنفسية في العجول (المونيميا هيمولتكا- باستريلا مالتوسيدا- هستوفلاس سيموني- ميكوبلازما بوفز) لمدة ٧ أيام وفي أنسجة الرئة لمدة ١٠أيام على الأقل خصوصا في العجول المحمومة.

SUMMARY

The present study was carried for studying the pharmacokinetic of tulathromycin in healthy and febrile feedlot calves. A single dose of tulathromycin (2.5 mg/kg b.w.) was injected subcutaneously to ten Friesian beef calves (5 healthy and 5 febrile) 4 to 6 months of age,

weighing 110 to 128 kg. Blood samples were collected after injection from all calves for determination of the concentrations of the drug by HPLC. Results showed that, the drug was rapidly absorbed reaching the highest plasma concentrations during 2 hours after dosing where C_{max}, $t_{1/2el}$, AUC and MRT was significantly higher in diseased (0.65h; 25.17h, 23.62 μg h ml^{-1} and 35.98h) than in healthy calves (0.59h; 24.14h, 20.78μg h ml^{-1} and 34.58h) respectively. Tulathromycin concentrations were maintained in the serum of injected calves equal to or higher than the MIC_{90} of major BRD pathogens (*Mannheimia haemolytica*, *Pasteurella multocida*, *Histophilus somni*, and *Mycoplasma bovis*) for about 7 days and in lung tissues at least 10 days especially in febrile ones.

Key words: *Tulathromycin, respiratory diseases, feedlot calves.*

INTRODUCTION

Bovine respiratory disease (BRD) is responsible for over 20% of pre-weaning and 50% of post-weaning calf deaths, for example annually; the U.S. feedlot industry faces enormous losses attributed to bovine respiratory disease (Martin *et al.*, 1989). Approximately 75% of the morbidity and up to 70% of the mortality observed in U.S. feedlot cattle is linked to BRD (USDA-APHIS, 1994; Edwards, 1996). Economic losses attributed to BRD includes death loss, therapeutic treatment cost (Martin *et al.*, 1982; Perino, 1992), performance loss (Bateman *et al.*, 1990; Morck *et al.*, 1993), and reduced carcass value (McNeill *et al.*, 1996; Larson, 2005). Management of this disease complex involves both metaphylactic and therapeutic administration of parenteral antimicrobials. Several studies have demonstrated the therapeutic efficacy of various antimicrobials, including florfenicol, tilmicosin, trimethoprim sulfadoxine, ceftiofur, and oxytetracycline, for the treatment of UF/BRD while few ones carried on tulathromycin (Jim *et al.*, 1992; Hoar *et al.*, 1998).

Tulathromycin is a triamilide antibiotic that maintains therapeutic concentrations for an extended period of time and approved for treatment of respiratory diseases in cattle and swine and is occasionally used in goats (Young *et al.*, 2011). Few studies shows that a single dose of tulathromycin is effective in treating cattle and swine

with respiratory disease and in preventing high-risk cattle from developing respiratory disease (Evans *et al.*, 2005). It is a new promising bactericidal semi-synthetic macrolide antibiotic specifically developed for the treatment and prevention of UF/BRD (Kilgore *et al.*, 2005; Nutsch *et al.*, 2005). And added it is highly effective, as a single antimicrobial dose indicated at high risk for control of BRD in cattle caused by *Mannheimia haemolytica*, *Pasteurella multocida*, *Histophilus somni*, and *Mycoplasma bovis*.

So this investigation was carried for studying the pharmacokinetic profiles of a single dose from tulathromycin; a novel antibacterial, when injected in healthy and febrile feedlot calves in maintaining serum level above MIC_{90} recorded for main BRD pathogens isolated from such infected calves for adequate time.

MATERIALS AND METHODS

A-Drug:-

Tulathromycin:- (Draxxin; Pfizer Ltd) a semi-synthetic macrolide antibiotic of the subclass; triamilide. Each mL of DRAXXIN contains 100 mg of tulathromycin, injectable solution indicated for the treatment of BRD. Its *in vitro* activity has been previously demonstrated against the main pathogens associated with BRD (Carbon, 1998).

B- Animals:-

Ten Friesian (5 healthy, 5 febrile, temp $\geq$ 40°C) beef calves 4 to 6 months of age, weighing 110 to 128kg, fed antibiotic free ration, not received any drug for at least three weeks were underwent to this study. All animals were injected once subcutaneously, by DRAXXIN (2.5 mg tulathromycin/kg BW).

C- Sampling:-

Blood samples were collected from all calves just prior to the drug injection, 1/2, 1, 2, 3, 6, 12, 18h, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 and 11 days post injection. Blood plasma was stored at –20°C until estimation of drug concentrations. Tulathromycin concentrations were measured by HPLC with UV detector with quantitation limits of 0.01 μg/ml according methods described by (Nowakowski *et al.*, 2004).

D- Statistical analysis:-

Statistical analysis was carried out using "t" test according to SAS (1999), and the kinetic parameters (C_{max}, t_{max}, $t_{1/2el}$, and AUC) were calculated according to Baggot (1977).

RESULTES

Tulathromycin concentrations in serum shown that the drug was rapidly absorbed reaching the highest plasma concentrations during two hours after dosing (Table1). Pharmacokinetic parameters for the drug used in this study were shown in Table (2).

Table 1: Mean tulathromycin plasma concentrations (μg/ml) following a single subcutaneous dose of Draxxin at 2.5mg/kg in healthy (n=5) and febrile (n=5)feedlot calves.

Time	Level in serum		Time	Level in serum	
	Healthy (n=5)	Febrile (n=5)		Healthy (n=5)	Febrile (n=5)
Pre-injection	ND	ND	3 day	0.09 ± 0.036	0.11±0.04
1/2h	0.43±0.08	0.45±0.08	4 day	0.082 ±0.028	0.086±0.03
1h	0.72±0.03	0.78±0.04	5 day	0.078 ± 0.007	0.080±0.02
2h	0.68 ± 0.039	0.72±0.03	6 day	0.06 ± 0.003	0.071±0.02
3h	0.62 ± 0.085	0.67±0.04	7 day	0.05 ± 0.004	0.058±0.008
6h	0.50 ± 0.041	0.52±0.04	8 day	0.041 ± 0.001	0.046±0.004
12h	0.35 ± 0.072	0.41±0.07	9 day	0.029 ± 0.005	0.033±0.007
18h	0.26 ± 0.072	0.28±0.06	10 day	0.016 ± 0.001	0.019±0.02
1 day	0.25 ± 0.064	0.26±0.06	11 day	ND	ND
2 day	0.16 ± 0.039	0.19±0.05			

Table 2: Pharmacokinetic parameters from noncompartmental analysis of tulathromycin following a single subcutaneous dose of Draxxin at 2.5mg/kg in healthy and febrile feedlot calves.

Parameters	Units	Healthy(n=5)	Febrile(n=5)
$t_{1/2}$	H	24.14 ±1.24	25.17 ± 1.33*
T_{max}	H	2.00 ± 0.45	2.00 ± 0.20
C_{max}	$\mu g\ mL^{-1}$	0.59 ± 0.04	0.65 ± 0.03*
$AUC_{0-\infty}$	$\mu g\ h\ ml^{-1}$	20.78 ± 2. 34	23.62 ± 1.85*
AUMC	$\mu g\ h^2\ ml^{-1}$	718 ± 1.88	850.15 ± 3.43**
Cl_B	(ml/h)/kg	0.12 ± 0.001	0.11 ± 0.001
B	µg/ml	0.59 ± 0.003	0.65 ± 0.004*
β	h^{-1}	0.028 ± 0.0001	0.027 ± 0.001
MRT	H	34.58 ± 2.06	35.98 ± 4.21*
Vc	$L\ kg^{-1}$	4.24 ± 0.52	3.85 ± 0.46*
$V_{d(area)}$	$L\ kg^{-1}$	4.30 ± 0.72	3.92 ± 0.55*

* $P< 0.05$; ** $P\leq 0.001$ when compared to healthy animals

N.B. The C_{max} (maximum plasma concentration) and T_{max} (time of maximum plasma concentration) were taken directly from the curve. $T_{½}$: is the half-lives of drug. T_{max}: time to peak concentration. C_{max}: maximum plasma concentration.; $AUC_{0-\infty}$: the area under the plasma concentration-time curve from zero to infinity. AUMC: area under the moment curve. Cl_B: total body clearance. B: zero time intercept of the regression line of the elimination phase. β: IS the first-order rate constants related to the elimination phases. MRT: mean residential time. V_c : volume of central compartment. $V_{d(area)}$: volume of distribution based on the total area under the plasma drug concentration time curve. **$p\leq 0.05$, ***$p\leq 0.001$.

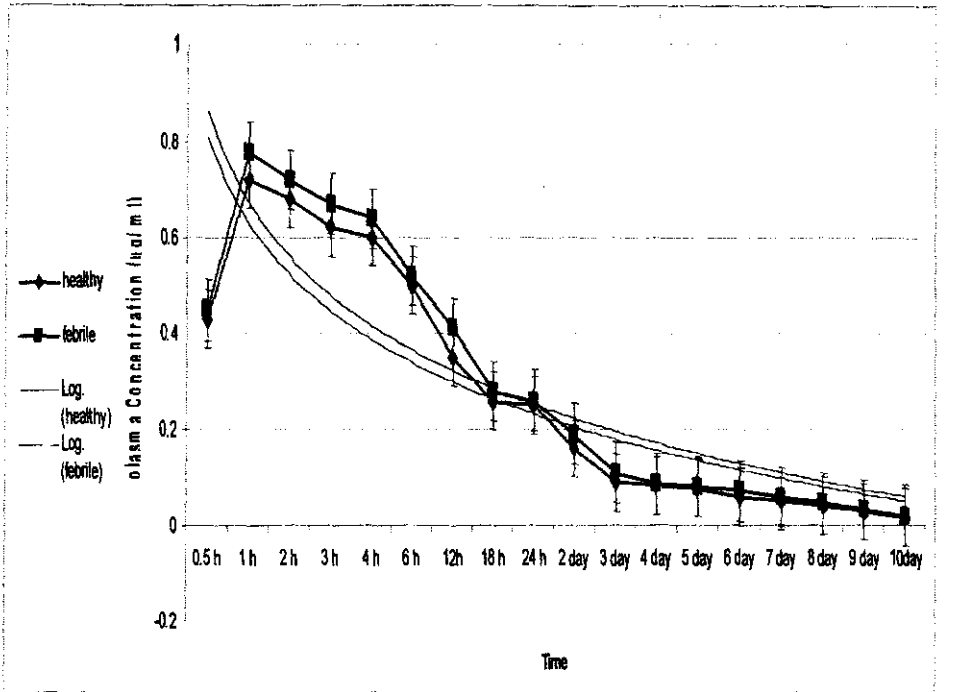

Fig. 1: Mean tulathromycin plasma concentrations (μg/ml) following a single subcutaneous dose of Draxxin at 2.5mg/kg in healthy (n=5) and febrile (n=5) feedlot calves.

DISCUSSION

Bovine veterinarians and beef cattle producers know there is no time to wait when a calf has BRD, especially valuable dairy replacement heifers, so they all time search for fast-acting, broad-spectrum BRD therapy killing major BRD-causing bacteria (*Mannheimia haemolytica, Pasteurella multocida* and *Histophilus somni* and *Mycoplasma bovis*) to be the first-line for treatment. And if a single dose is sufficient to save time, labor, costs, reduces animal stress as well as the risk of workers and animals in such cases it considered a drug of choice. So Draxxin as a single dose, fast-acting and broad-spectrum BRD therapy may consider an ideal option in such cases.

The present study showed that tulathromycin was rapidly absorbed and during two hours after dosing reaching the highest plasma

concentrations which significant higher in febrile than in healthy calves where C_{max} was 0.65 ± 0.03 and 0.59 ± 0.04 μg mL^{-1}, while T_{max} were 2.00 ± 0.20 and 2.00 ± 0.45h in febrile and healthy calves respectively. Nearly similar results in healthy calves were recorded by Young *et al.* (2011) where they recorded C_{max} 0.633±0.3 μg /ml and Cox *et al.* (2010) where T_{max} was 3h. But the present results were not completely similar to that reported by Evans *et al.* (2005) where they found C_{max} 0.489μg/ml but T_{max} was shorter (0.5h) after injection of tulathromycin to feeder calves 2.5 mg /kg b.w. And added linear pharmacokinetics for tulathromycin is observed, rapid release and absorption from the injection site, extensive distribution and slow elimination. Furthermore, in this study $t_{1/2el}$ was 25.17 ± 1.33 and 24.14 ±1.24 in febrile and healthy calves respectively that shorter than results of Cox *et al.* (2010) for $t_{1/2el}$ that was 64 h; Evans *et al.* (2005) where $t_{1/2el}$ 2.75 days and EMEA (2004) recorded $t_{1/2el}$ more than 70 hours for tulathromycin in plasma of healthy calves.

The disease conditions are known to markedly alter the disposition of antimicrobials (Burrows, 1985). Fever is one of the most common manifestations of infectious diseases and is reported to induce biochemical and physiological alterations in the cells (Van-Miert, 1987; Lohuis *et al.*, 1988). It may affect the absorption, distribution, and elimination of drugs and these changes in pharmacokinetics vary with the animal species, antibiotic and agent that cause a febrile reaction (Bojana, 1999). This study illustrated, $t_{1/2el}$, AUC and MRT was significantly higher in diseased (25.17h, 23.62 μg h ml^{-1} and 35.98h) than in healthy calves (24.14h, 20.78μg h ml^{-1} and 34.58h). These significant variations between $t_{1/2el}$, AUC and MRT in febrile and healthy calves in the present study were in agreement with the results of Ismail and El-Kattan (2007) following i.m. administration of marbofloxacin in healthy and *Mannheimia haemolytica* infected calves. They found $t_{1/2el}$, AUC and MRT were significantly longer in diseased calves (8h, 22.24μg h ml^{-1} and 12h) than in healthy ones (4.7h; 12μg h ml^{-1} and 7.4h), respectively. They added the C_{max}/MIC and AUC_{24}/MIC ratios were significantly higher in diseased (13.0–64.4 and 125–618 h) than in healthy calves (8–38.33 and 66.34–328 h). And concluded (C_{max}/MIC, AUC/MIC and T ≥ MIC) indicate the excellent pharmacodynamic characteristics of the drug in diseased calves, which can be expected to optimize the clinical efficacy and minimize the development of resistance. Moreover, the present findings are consistent

with those reported for other fluoroquinolones in febrile goats (Jha *et al.*, 1996; Rao *et al.*, 2000), but it was inconsistent with that reported in *M. haemolytica* infected calves treated with erythromycin (Burrows, 1985). In this respect Baggot (1980) mentioned that the elimination half-life ($t_{1/2b}$) and mean residence time (MRT) of marbofloxacin were longer in pneumonic calves than in healthy ones. This delay in the elimination of the drug may be the result of renal and/or hepatic abnormalities caused by fever and endotoxin production accompanied with *M. haemolytica* infection (Hodgson *et al.*, 2003). Endotoxin produces direct tubular cell injury as well as some functional changes in the kidney, including a decrease in the renal blood flow and glomerular filtration rate, and changes the intrarenal hemodynamics (Jernigan *et al.*, 1988). In addition, endotoxin causes metabolic acidosis and reduces urinary pH in febrile animals (Baggot, 1980; Salam Abdullah and Baggot, 1984; Spurlock *et al.*, 1985; Van-Miert, 1990). It is probable that the decrease in glomerular filtration rate and metabolic acidosis induced by endotoxin plays an important role in the reduction of body clearance of marbofloxacin and consequently increases its elimination half-life (Waxman *et al.*, 2003). This decrease in body clearance has been previously observed for danofloxacin and marbofloxacin in pneumonic calves (Apley and Upson, 1993; Thomas *et al.*, 1994b).

As previously known, the main four pathogens associated with BRD feedlot calves are *Mannheimia haemolytica, Pasteurella multocida, Histophilus somni* and *Mycoplasma bovis* (Mosier, 1997; Carbon 1998; Donachie, 2000; Loneragan *et al.*, 2001; Ames *et al.*, 2002; Nicholas and Ayling, 2003). And its recorded MIC_{90} with tulathromycin are 2.0, 1.0 and 0.5-2μg/ml (Nightingale, 1997; Godinho *et al.*, 2005a; Kilgore *et al.*, 2005) and 1μg/ml (Godinho *et al.*, 2005b; Kilgore *et al.*, 2005) respectively.

In vitro the activity of tulathromycin was demonstrated by Carbon (1998) against *Mannheimia haemolytica, Pasteurella multocida, Histophilus somni* and *Mycoplasma bovis*. *In vivo* the clinical efficacy of tulathromycin was documented by Nutsch *et al.* (2005); Rooney *et al.* (2005); Skogerboe *et al.* (2005) in their studies for control and treatment of BRD in cattle caused by *Mannheimia haemolytica, Pasteurella multocida, Histophilus somni and Mycoplasma bovis* and concluded accumulation of tulathromycin in lung tissues. Previously, Nightingale (1997) noted extensive distribution for tulathromycin into body tissues;

especially in lung tissues, EMEA (2004) recorded $t_{1/2el}$ in plasma more than 70 hours versus 8 days for lung tissue and concluded this was evident from lung/plasma concentration ratios and indicated accumulation of the drug in lung tissues. Likewise Evans *et al.* (2005) recorded C_{max} 0.489 and 4.1μg/ml, $t_{1/2el}$ 2.75 and 8.75 days and AUC_{0-48h} was 16.7 and 1230 μg-h/ml in serum and lung tissues (the therapeutic target organ) of cattle respectively and $lung_{AUC}/plasma_{AUC}$ was 73.7 ratio. They attributed this long elimination half-life to extensive volume of distribution (more than 10 l/kg) for this drug which has linear pharmacokinetics characters. Likewise Galer *et al.* (2004); Nowakowski *et al.* (2004) detected the therapeutic concentrations of tulathromycin in lung tissue for 10 to 15 days after a single dose.

Based on the present study and all these mentioned results, the expected levels in lung tissues for tulathromycin were maintained equal to or higher than MIC_{90} of major BRD pathogens (specially in fibril calves) at least 10 days or more that considered enough for treating BRD caused by that bacteria sensitive *in vitro* to the drug. This expectation supported by Nowakowski *et al.* (2004) when said the apparent elimination half- life of tulathromycin in bovine lung tissue is 8 days, and mean concentrations of approximately 3.0, 1.9, and 1.2 μg/g were attained at 7, 10, and 15 days, respectively.

Although the relationship between tulathromycin and the characteristics of its antimicrobial effects has not been characterized, as a class, macrolides tend to be primarily bacteriostatic, but may be bactericidal against some pathogens Nightingale (1997). They also tend to exhibit concentration independent killing; the rate of bacterial eradication does not change once serum drug concentrations reach 2 to 3 times the MIC of the targeted pathogen. And added under these conditions, the time that serum concentrations remain above the MIC becomes the major determinant of antimicrobial activity. Furthermore, macrolides also exhibit a post-antibiotic effect (PAE), the duration of which tends to be both drug and pathogen dependent. So by increasing the macrolide concentration and the exposure time, the PAE will increase to some maximal duration and these two variables, concentration and exposure time, drug concentration tend to be the most powerful determinant of the duration of PAE (Nightingale, 1997).

Finally can concluded, the drug has a big advantage of the lack of daily handling of the animal with good serum and lung tissues

concentrations (about 10 days or more in lung tissues especially in fibril ones) when injected once as a single dose. In keeping with this line, Schnepper, (2006) concluded a single subcutaneous dose of Draxxin will produce an antibiotic level in lung tissues for up to 15 days. This makes it very appealing to the producer, to be able to give one injection upon arrival at a facility and the antibiotic last for 15 days. And added Draxxin goes through a needle very easily and the product is stable at room temperatures for 36 months. Evans *et al.* (2005); Godinho *et al.* (2005b); Technical Bulletin (2006) concluded a single dose of DRAXXIN® (tulathromycin) injectable solution the only antibiotic approved and highly effective for treatment of BRD associated with *Mycoplasma bovis*. Technical Bulletin (2006) concluded the DRAXXIN® (tulathromycin) injectable solution administered as a single subcutaneous injection was safe and effective for the treatment of experimentally induced *Mycoplasma bovis* respiratory infection in calves.

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