Pharmacokinetic And Pharmacodynamic Studies Of Tulathromycin In Buffalo Calves

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ABSTRACT

The response of pneumonic buffalo calves to therapy with tulathromycin was evaluated in a private farm in Zagazig city, Sharkia Province. A total number of 16 calve 3-9 months old (11clinically healthy calves and 5 pneumonic calves) were used in this investigation. Ten buffalo calves were classified into 2 equal groups each of 5 calves, 1st group were healthy calves (control group) and 2nd group calves were suffered from pneumonia treated with tulathromycin. Blood samples were collected for stydying the effect of tulathromycin treatment on biochemical parameters of pneumonic calves. Pharmacokinetics of tulathromycin were studied after single dose I/V, I/M and S/C injection. Six apparently healthy buffalo calves were used in a crossover design.

Pneumonic calves showed significant decrease in total proteins, albumin, globulin, and significant increase in AST, ALT, total bilirubin, glucose urea and creatinine . Ca was insignificantly decreased, meanwhile Na and K were insignificantly increased. Biochemical parameters were returned to the their normal levels on 15 days post treatment.

After I/V injection of tulathromycin, half-lives of distribution and elimination ($t_{0.5\ (\alpha)}$ and $t_{0.5\ (\beta)}$), volume of distribution at steady state (Vd), and total body clearance (Cl_B) were 0.17 h., 48.35 h., 4.25 L kg^{-1}., and 0.06 L kg^{-1} h^{-1}, respectively. Following I/M and S/C tulathromycin injection, maximum concentration (C_{max}) 0.33 and 0.31ug ml^{-1} were achieved at a maximum times (t_{max}) 1.12 and 1.23h., respectively. The mean values for absorption and elimination half-lives ($t_{0.5(ab)}$ and $t_{0.5(el)}$) and MRT were 0.14 and 0.16 h., 68.93 and 65.87 h., 99.56and 95.17h respectively. The I/M and S/C bioavailabilities were 82.8 and 71.9% respecti- vely. Result of *in-vitro* protein-binding study indicated that 38.9% of tulathromycin was bound to calves serum proteins.

It could be concluded that treatment by tulathromycin induce disappepearance of the clinical signs of pneumonia in buffalo calves and biochemical parameters returned to their normal levels.

INTRODUCTION

Pneumonia is a major problem in buffalo calves it represents most important cause of calve mortality that leads to severe economic losses *(1)*. Bovine respiratory disease is important cause of mortality in calves *(2)*. The condition involves a complex of different etiologies, including various viral, mycoplasmal, and bacterial pathogens, and susceptability is potentiated by stress factors *(3)*. Buffaloes have sort of resistance against infection compared with other domestic live stock *(4)*.

Macrolide antibiotics are active agents against *G+ve* bacteria act on bacterial ribosome inhibiting bacterial protein synthesis *(5)*. Tulathromycin is a long acting semisynthetic macrolide used in respiratory infections *(6)*, with large volum of distribution *(7)*, long elimination half-life **(8)** and high concentration in lung tissue after I/M injection in cattle *(9)*. Tulathromycin rapidly absorbed and widely

distributed and has a long elimination half-life in lung tissue *(7)*, the *in vivo* activity of tulathromycin has been confirmed in a murine model of respiratory infection and in cattle *(10)*.

The present study was carried out to throw the light on the efficacy of tulathromycin in pneumonic calves. Special attention was paid to its pharmacokinetic.

MATERIAL AND METHODS

Drug

Tulathromycin (Draxxin) ® injectable solution produced by Pfizer Company, Cairo, Egypt. It contains 100 mg ml^{-1}

Animals

This study was carried out at a private farm in Zagazig city, Sharkia Province. A total number of 16 buffalo calve aged from 3-9 months old was involved in this investigation (11 clinically healthy and 5 Pneumonic calves). All animals were feed on barseem and dry ration and water was supplied *ad libitum*. Pneumonic calves showed some or all clinical signs of pneumonia, including fever, cough, dullness, an increase in pulsation and respiration rates, lake of appetite, nasal flaring, mandibular lymph node enlargement and respiratory difficulties.

Experimental designs

Effect of tulathromycin in pneumonic calves

Ten buffalo calves were classified into 2 equal groups each of 5 calves, 1st group were healthy calves (control group) and 2nd group calves were suffered from pneumonia and treated single S/C with tulathromycin 2.5 mg/ kg B. wt. Blood samples were collected from both groups by jugular vein puncture before and on 1, 7 and 15 days post treatment to obtain clear serum for estimation of ca, k, total bilirubin, Na, glucose level AST and ALT *(11)*, T. proteins *(12)* serum albumin *(13)*, globulin was calculated as difference between total proteins and albumin, uric acid *(14)* creatinine *(15)*.

Experimental protocol for pharmacokinetic

Six apparently healthy, buffalo calves of both sex (3-9 months old and mean body weight of 98-123 kg) were used for pharmacokinetic study. All six calves were administered 2.5 mg kg^{-1} tulathromycin *(16)* by I/V, I/M and S/C route with a 2 weeks washout period between each route of injection. Blood samples were collected via vein puncture from jugular vein before and 0.083, 0.167, 0.25, 0.5, 1, 2, 4, 6, 8, 10, 12, 24, 48, 72, 96 and 120 hours post-injection. Blood samples were left to clot then centrifuged at 3000 revolution per minute for 15 minutes to obtain clear serum that was kept frozen at -20 °C until assayed.

Drug bioassay

Samples were assayed by microbiological assay *(17)* using *Micrococcus luteus* (ATCC 9341). Determination of antibiotic concentration is commonly carried out by microbiological assays, but they are often lengthy and lack the specificity and precision required for regulatory purposes *(18)*. Standard tulathromycin concentrations of 0.156, 0.3125, 0.625, 1.25, 2.5, 5 and 10ug ml^{-1} were prepared in antibiotic-free calf serum and phosphate buffer saline (pH 8). The minimal detectable limit for the assay method was 0.156 ug ml^{-1}.Semi-logarithmic plots of inhibition zone diameter versus standard tulathromycin concentrations in serum and phosphate buffer were linear with typical correlation coefficient of 0.998 (for the standard curve). The difference of inhibition zone diameter between the solutions of the drug in serum and buffer was used to calculate the *in-vitro* protein binding tendency of tulathromycin by the following equation *(19)*:

$$\text{Protein binding \%} = \frac{\text{Zone of inhibition in buffer-Zone of inhibition in serum}}{\text{Zone of inhibition in buffer}} \times 100$$

Pharmacokinetic analysis

Serum concentrations of tulathromycin for each individual calf after IV, IM and SC administrations were subjected to a compartmental analysis using a nonlinear least-squares regression analysis with the help of a computerized curve-stripping program (R Strip; Micromath Scientific Software, Salt Lake City, UT, USA). For IV, IM and SC data, the appropriate pharmacokinetic model was determined by visual examination of individual concentration-time curves and by application of Akaike's Information Criterion (AIC) *(20)*. Following IV injection, the serum concentration-time relationship was best estimated as a two-compartment open model system *(21)* according to the following bi-exponential equation: $Cp = Ae^{-\hat{a}t} + Be^{-\hat{a}t}$, where Cp is the concentration of drug in the serum at time t; A is the intercept of the distribution phase with the concentration axis expressed as ug ml^{-1}; B is the intercept of the elimination phase with the concentration axis expressed as ug ml^{-1}; α is the distribution rate constant expressed in units of reciprocal time (h^{-1}); β is the elimination rate constant expressed in units of reciprocal time (h^{-1}); and e is the natural logarithm base. After IM and SC administration, data was analyzed by adopting a one-compartment open model. This program also calculated non compartmental parameters using the statistical moment theory *(22)*. The C_{max} (maximum serum concentration) and t_{max} (time of maximum serum concentration) were taken directly from the curve. The terminal elimination half-life ($t_{0.5\ (el)}$) and absorption half-life ($t_{0.5\ (ab)}$) were calculated as $\ln 2/K_{el}$ or $\ln 2/K_{ab}$, respectively, where K_{el} and K_{ab} are the elimination and absorption rate constants, respectively. The area under serum concentration-time curve (AUC) and area under the first moment curve (AUMC) were calculated by the method of trapezoids and extrapolation to infinity was performed. The mean residence time (MRT) and mean absorption time (MAT) were calculated as MRT = AUMC/AUC and MAT = $MRT_{i.m} - MRT_{i.v}$. The total body clearance (ClB) was calculated as ClB = Dose/AUC and the absolute bioavailability (F) as $F = AUC_{i.m}/AUC_{i.v} \cdot 100$.

Statistical analysis: obtained data was analyzed *(23)*.

RESULTS AND DISCUSSION

Pneumonic calves showed clinical signs as fever, cough, dullness, increase pulse, loss of appetite, nasal discharge, conjuctival hyperemia and difficult respiration. Same clinical signs were recorded in calves *(24)*.

Data presented in Table 3 showed a significant increase in transaminases (AST and ALT), total bilurbin and significant decrease in total proteins, albumin and globulins. Buffalo – calves suffering from pneumonia showed significant increase in AST and ALT and Total bilurbin *(25)*. Similar results were reported in pneumonic sheep *(26)*, in goats by *(27)* and in calves *(28)*. Reduction in protein profile may be due to anorexia and inability of liver to synthesis albumin *(29)*. The decreased in globulin in pneumonic calves in our study was similar to those reported *(30)* which showed that the decrease in beta globulin in pneumonic lambs is due to liver disease. Also, decrease liver albumin synthesis may be associated with possible hepatocellular dysfunction induced by inflammation *(31)*.

Statistical analysis of the obtained result showed a highly significant decrease elevatio in serum glucose, urea and creatinin insignificant decrease in calcium ar insignificant increase in sodium and potassiu (table 4). Same results were recorded pneumonic lambs *(32)*. Elevation in urea a creatinine in pneumonic calves may be due increase protein catabolism and decreased re blood flow which might occur in cases pneumonia which tend to increase urea a creatinine levels *(33)*. Our results were sim to those previously recorded *(34)*. Ser calcium was insignificantly decreased pneumonic calves *(35)*. Potasium and sod

levels were insignificantly increased in pneumonia lamb *(36)*.

Treatment of pneumonic calves with S/C with tulathromycin 2.5 mg/ kg b. wt. at single dose revealed that the cure rate was 100% on 3 day post treatment, clinical signs disappeared and biochemical parameters returned to nearly their normal level on 7th day post treatment these findings were similar to that previously reported by *(37)*.

Disposition of tulathromycin in buffalo calves serum after I/V injection was best described by the two-compartment open-pharmacokinetic model. Tulathromycin was rapidly distributed with a short distribution half-life ($t_{0.5(\alpha)}$) of 0.17 h. Similarly, rapid distribution had been recorded for the tylosin in sheep and goats (0.143 and 0.213 h) *(38)*. The apparent volume of distribution at steady-state (V_{dss}) is an accurate indication of the diffusion of the drug into the body tissues *(39)*. The result of this study revealed that tulathromycin was widely distributed to extra-vascular tissues as indicated by larger volumes of distribution at steady-state (V_{dss}) 4.25L kg^{-1}. Tulathromycin is widely distributed and its elimination is extremely slow with half-life 4-6 days *(8)*. The drug was widely distributed with volumes of distribution at equilibrium ranging between 12.7 and 18.2 L kg^{-1} and slowly eliminated with half-life 101-158 h *(40)*.

Serum concentration-time curves describing the disposition of tulathromycin after I/M and S/C injection were remarkably similar, as recorded for Cmax, tmax, $t_{0.5\ (ab)}$ and $t_{0.5\ (el)}$. In this study, tulathromycin achieved a maximal concentrations (Cmax 0.33and 0.31ug ml^{-1}), relatively close to that in foals (0.410 ug ml^{-1}) *(40)* but lower than that in pigs (0.616 ug ml^{-1}) *(8)*. Differences in kinetic parameters are relatively common and are frequently related to interspecies variation, age, breed, health status of the animals and/or the assay method used *(41)*. Absorption was rapid after I/M and S/C injection of the drug as indicated by large absorption rate constant (kab) 5.15 and 4.46 h^{-1} and short absorption half-life ($t_{0.5(ab)}$) 0.14and 0.16 h., respectively. Following a single S/C injection, the drug was rapidly absorbed *(7)*. Tulathromycin was slowly eliminated from the body as evidenced by long elimination half life ($t_{0.5\ (el)}$) and mean residence time (MRT) 68.93 and 65.87 h., 99.56 and 95.17h., respectively. The values of systemic bioavailability of tulathromycin after I/M injection 82.8 % indicated good absorption of the drug from the site of I/M injection. The I/M systemic bioavailability has been reported to be 87 % in pigs *(8)*. Tulathromycin after I/M administration is rapidly and nearly completely absorbed from the injection site to reach maximal serum concentrations within 1h *(40)*. The *in vitro* protein binding tendency of tulathromycin to buffalo calves serum proteins was 38.9%. For another macrolide antibiotic (clarithromycin and azithromycin) this value ranged from 7-50 % *(42)*. The minimum inhibitory concentrations (MICs) for tulathromycin against isolated bovine and porcine respiratory pathogens (*Mannheimia haemolytica, Pasteurella multocida, Mycoplasma bovis* and *Mycoplasma hypopneumoniae*) were previously reported to be 0125-0.25 ug ml^{-1} *(43)*. The serum concentration of tulathromycin following I/V, I/M and S/C injection was higher than the MIC for the previously mentioned bacteria. This result indicates that tulathromycin could be used successfully for treatment of such types of bacterial infection in calves.

It could be concluded that tulathromycin cause the disappearance clinical signs of pneumonia in buffalo calves and biochemical parameters were returned to their normal levels.

Table 1. Efficacy of tulathromycin(2.5 mg/ kg b. wt. at single dose SC) in treatment of pneumonic calves

Total No. of treated calves	Days post treatment					
	1		3		6	
	No. cured calves	%	No. cured calves	%	No. cured calves	%
5	2	40	3	100	-	-

Table 2. Clinical signs of pneumonic calves pre and post treatment with tulathromycin(2.5 mg/ kg b. wt. at single dose SC) (n=5)

parameter	Healthy calves	Diseased calves			
		Pre treatment	Post treatment		
			1st day	7th day	15th
Temperature	38.6±0.4	40.63±0.59	39.43±0.85	38.89±0.83	38.71±0.91
Respiratory rate	22.21±5.20	35.53±5.33	30.52±6.41	25.2±4.77	23.04±3.34
Pulsation	79.73±4.41	90.8±9.85	87.9±8.53	84.8±7.21	80.02±6.41
Rumen moving	2.68±0.22	1.32±0.31	2.01±0.20	2.53±0.18	2.80±0.24
Nasal discharge	normal	Seromucous-mucous	normal	normal	normal
conjactiva	normal	hyperemic	Slight hyperemic	normal	normal
Lung auscultation	normal	Miost rale- dry rale	normal	normal	normal

Table 3. Liver function test in pneumonic calves before and after treatment of tulathromycin(2.5 mg/ kg b. wt. at single dose SC) (n=5)

parameter	Healthy calves	Diseased calves			
		Pre treatment	Post treatment		
			1st day	7th day	15th
AST (U/L)	29.38 ±0.68	32.08 ±0.60*	31.84±0.36*	30.73±0.59	29.89 ±0.40
ALP(U/L)	19.42±0.35	21.10±0.54*	20.80±0.40*	20.41±0.52	19.68±0.43
Total bilirubin	0.2±0.07	0.5±0.09*	0.4±0.03*	0.35±0.06	0.3±0.07
Total proteins (gm/dl)	7.10±0.42	4.4±0.52**	5.73±0.31*	6.48±0.46	6.99±0.57
Albumin (gm/dl)	4.10±0.12	2.35±0.69*	3.40±0.21*	3.75±0.23	3.90±0.63
Globulins (gm/dl)	3.00±0.21	2.05±0.30*	2.33±0.23*	2.73±0.22	3.09±0.59
A/G Ratio	1.09±0.18	1.15±0.22	1.03±0.17	1.37±0.20	1.26±0.26

Table 4. Kidney function test and glucose in pneumonic calves before and after treatment of tulathromycin (2.5 mg/ kg b. wt. at single dose SC) (n=5)

Parameter	Healthy calves	Diseased calves			
		Pre treatment	Post treatment		
			1st day	7th day	15th
Glucose (mg/dl)	67.44±1.21	71.28±1.12*	70.87±0.97*	68.21±0.89	67.78±0.94
Urea (mg/dl)	15.90±0.27	18.10±0.76*	17.83±0.59*	16.58±0.79	15.99±0.84
Creatinine (mg/dl)	1.48±0.14	2.07±0.11*	1.99±0.10*	1.86±0.13	1.59±0.14
Calcium	11.64±1.24	10.53±1.12	10.98±1.49	11.08±1.43	11.52±1.42
Sodium	135.23±2.53	133.62±1.45	133.98±1.70	134.53±1.69	135.12±1.45
Potassium	6.32±0.95	7.17±0.82	6.94±0.59	6.66±0.73	6.42±0.64

Table 5. Mean (± S.E) kinetic parameters of tulathromycin in buffalo calves following a single I/V injection of 2.5 mg kg-1 b.wt (n=6).

Parameter	Unit	IV injection
Cp^0 concentration at zero time (immediately after single IV injection)	ug ml-1	0.83±0.04
A(zero-time intercepts of the biphasic disposition curve)	ug ml-1	0.26±0.07
B(zero-time intercepts of the biphasic disposition curve)	ug ml-1	0.57±0.03
α(hybrid rate constants representing the slopes of distribution phases)	h-1	4.17±0.22
β(hybrid rate constants representing the slopes of elimination phases)	h-1	0.01±0.002
K12(first-order constant for transfer from central to peripheral compartment)	h-1	1.28±0.06
K21 (firstorder constant for transfer from peripheral to central compartment)	h-1	2.89±0.06
Kel (elimination rate constant)	h-1	0.02±0.008
t0.5(α) (distribution half-life)	h	0.17±0.06
t0.5(β) (elimination half-life)	h	48.35±2.3
Vc (apparent volume of the central Compartment)	L kg-1	3.03±0.14
Vdss (volume of distribution at steady state)	L kg-1	4.25±0.28
ClB (total body clearance)	L kg-1 h-1	0.06±0.007
MRT(mean residence time)	h	69.65±5.1
AUC (area under serum concentration-time curve)	ug ml-1 h-1	40.95±3.1
AUMC (area under moment curve)	ug ml-1 h-1	2774.0± 215.1

Table 6. Mean (± S.E) kinetic parameters of tulathromycin in buffalo calves following a single I/M and S/C injection of 2.5 mg kg-1 b.wt (n=6)

Parameter	Unit	Intramuscular (IM)	Subcutaneous (SC)
Cmax (maximum serum concentration)	ug ml-1	0.33+0.02	0.31±0.06
Tmax(time to peak serum concentration)	h	1.12+0.10	1.23±0.17
Kab(first-order absorption rate constant)	h-1	5.15+0.34	4.46±0.41
Kel (elimination rate constant)	h-1	0.01+0.006	0.01±0.004
t0.5(ab)(absorption half-life)	h	0.14+0.07	0.16±0.04
t0.5(el)(elimination half-life)	h	68.93+4.6	65.87±5.3
AUC (area under serum concentration-time curve	ug ml-1 h-1	33.91+2.3	29.42±4.2
AUMC (area under moment curve)	ug ml-1 h-2	3309.2+227.6	2832.8±277.1
MRT(mean residence time)	h	99.56+6.9	95.17±7.3
MAT(mean absorption time)	h	29.92+1.9	25.52±2.6
F(fraction of drug absorbed systemically)	%	82.8+5.7	71.9±6.7

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الملخص العربى

دراسات فارماكوكينيتكية وفارماكوديناميكية للتيلاثيروميسن في عجول الجاموس

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لدراسة تأثير التلاثروميسين على العجول الجاموسى المصابة بالالتهابات الرئوية ١٦ عجل عمر من ٣ الى ٩ شهور بأحد المزارع الخاصة بمدينه الزقازيق محافظه الشرقيه (١١ بصحة جيده -٥ تعانى من وجود التهاب رئوي) تم تقسيم ١٠ عجول إلى مجموعتين كلا منها يحتوى على ٥ عجول. المجموعة الاولى سليمة (محكمة) والثانية عجول مصابه بالالتهاب الرئوي وتعالج بجرعه واحده من التلاثروميسين بجرعة واحدة بمعدل ٢,٥ مجم تحت الجلد. تم تجميع عينات دم من العجول قبل العلاج 1 و٧ و ١٥ يوم بعد العلاج لقياس بعض الوظائف البيوكيميائيه.

تم دراسة مسار الدواء (الفارماكوكينتيك) لعقار التلاثروميسين بعد الحقن بجرعة واحدة بالوريد و العضل وتحت الجلد مع مراعاة ترك فترة من الوقت تصل إلي ١٥ يوم بين الجرعات لضمان خروج الدواء من الجسم . لهذا الغرض تم استخدام ٦ عجول جاموس سليم ظهريا .

أظهرت النتائج إن الالتهابات الرئوية أدت إلي حدوث نقص معنوي في البروتين الكلي ، الالبيومين الجلوبيولين ، زيادة معنوية في نشاط الامينوترنزفيراسس(AST, ALT), البيلوربين الكلى, الجلوكوز, اليوريا والكرياتينين . كما أدى إلي نقص معنوي في الكالسيوم وزيادة غير معنوية في مستوى البوتاسيوم والصوديوم . كما لوحظ أن أستخدام التلاثروميسين أدي إلي تناقص في درجة الحرارة (الحمي) و اختفاء الأعراض التنفسية وعودة هذه الوظائف إلي المستوى الطبيعي في مصل العجول المصابة والمعالجة .

بعد الحقن بالوريد وجد أن فترة عمر نصف العمر للانتشار($t_{0.5(\alpha)}$) وفترة عمر نصف العمر الإخراج ($t_{0.5(\beta)}$), وحجم التوزيع,(Vd_{ss}) وكمية الإخراج (Cl_B) كانت ٠,١٧ ساعة ، ٤٨,٣٥ ساعة، ٤,٢٥ لتر/كجم،٠,٠٦ لتر/كجم على التوالي.

بعد الحقن بالعضل وتحت الجلد لعقار التلاثروميسين كان أعلى تركيز للدواء (C_{max}) ٠,٣٣ ، ٠,٣١ ميكرو جرام وصل عند أقصى وقت (t_{max}) ١,١٢ ، ١,٢٣ ساعة على التوالي . وكانت فترة نصف العمر الامتصاص ($t_{0.5(ab)}$) وفترة نصف العمر الإخراج ($t_{0.5(el)}$) وMRT ٠,١٤ ، ٠,١٦ ،٦٥,٨٧ ، ٩٩,٥٦ ، ٩٥,١٧ ساعة على التوالي . وكانت الاتاحة الحيوية (مدى كفاءة الامتصاص) بعد الحقن بالعضل وتحت الجلد ٨٢,٨ ، ٧١,٩ % على التوالى . وكانت نتيجة دراسة ارتباط التلاثروميسين مع بروتين مصل الجاموس خارج الجسم ٣٨,٩ % .