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### Pharmacokinetic evaluation of co- administration of Triclabendazole and Tildipirosin in goats

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#### ABSTRACT

The existing research aimed to explore triclabendazole effect (10 mg/kg b.wt., orally ) on disposition kinetic of tildipirosin (4 mg/kg b.wt) administered by intravenous or intramuscular routes in goats. Serum tildipirosin concentration was measured using microbiological technique by *Bacillus subtilis*. The concentration-time curve of tildipirosin was described via two compartment open model. Concomitant administration with triclabendazole decreased tildipirosin concentrations in serum post IV and IM injection.

After IV administration, serum tildipirosin concentration at zero time ( $C_0$ ) showed lower in the triclabendazole pretreated goat group. The administration of triclabendazole significantly increased the tildipirosin distribution rate constant ( $\alpha$ ), the apparent peripheral compartment volume ( $V_2$ ); distribution volume at steady state ( $V_{dss}$ ), total body clearance (CL) and inter-compartmental clearances (CL<sub>2</sub>) in the second group compared with first group. On the other hand, triclabendazole potentially reduced the half-life of distribution ( $t_{1/2}$  Alpha), half- life of elimination ( $t_{1/2}$ Beta), area under curve (AUC<sub>0-t</sub>), and mean residence time expressed as MRT in the triclabendazole co-administered group.

Following intramuscular injection, absorption half-life and corresponding  $t_{max}$  exposed fast tildipirosin absorption rate. Maximum serum concentration ( $C_{max}$ ) and area under the curve of tildipirosin showed significant decline of triclabendazole co-administered group compared with tildipirosin alone. Both  $t_{1/2}$  beta and MRT were decreased post I/M injection in the tildipirosin-triclabendazole group. Simultaneous administration of triclabendazole and tildipirosin caused significant variations in tildipirosin disposition kinetic. The interactions between the two drugs have clinical importance and so require tildipirosin dosage monitoring.

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## INTRODUCTION

Macrolides are bacteriostatic drugs for vast majority of microorganisms because of their attachment to ribosomal ribonucleic acid at the 23S of the bacterial cell's ribosomal subunits (50S) that restricting protein synthesis. Tildipirosin has 16-membered ring that has been authorized in macrolide veterinary medicine for cattle, pigs, sheep, rabbits and horse respiratory disease treatment (Bartram et al. 2016 Confer et al. 2016 Lei et al. 2018; Xiong et al. 2020; Abu Basha et al. 2021).

Tildipirosin has been found to have a bacteriostatic impact on *B. bronchiseptica* and *P. multocida*, as well as a bactericidal action against *H. somni*, *M. haemolytica* and *A. pleuropneumoniae* and also *H. parasuis* in in vitro experiments. Cattle, mice, rabbits and dogs have all been studied for tildipirosin pharmacokinetics and proved that tildipirosin had extended half-life and high bioavailability following extra vascular injection in these trials (Torres et al. 2016 Teixeira et al. 2017 Arsic et al. 2018 Zeng et al. 2018 EMA 2020).

Anthelmintic drugs are currently the major method for managing parasite infections. Nevertheless, the growth of drug-resistant portends treatment efforts. Triclabendazole (TCBZ) is a novel benzimidazole medication that works against *Fasciola hepatica* and *Fasciola gigantica* (mature and immature stages) of cattle, sheep and goat (Sanyal 1994; Mottier et al. 2004). The oxidized metabolites of triclabendazole include triclabendazole sulphoxide, triclabendazole sulphone, and keto triclabendazole showed efficient effects against parasite (Halferty et al. 2009 Belal et al. 2014 Robles-Pérez et al. 2015 Wang et al. 2019).

Medication combinations are widely used in veterinary medicine. These tested combinations in goats exhibited either pharmacological potentiation or decreased effect (Sidhu et al. 2006 Gould 2016). In veterinary medicine, minimum attention has been paid to the pharmacokinetic interactions of anthelmintic with antibacterial drugs. To date, there is no data on the pharmacokinetics of compiled tildipirosin with triclabendazole treatment in goats. Thus,

the objective of this research was to appraise the influence of oral triclabendazole administration on intravenous (IV) and also intramuscular (IM) administration of tildipirosin pharmacokinetic in goats.

## MATERIALS and METHODS

### Drugs and Chemicals:

Tildipirosin (Zuprevo® ,solution containing 180 mg/ml) was obtained from Intervet, Netherlands.

Triclabendazole (tricazanamed®, suspension containing 100 mg/ml ) was obtained from Sigma Pharmaceutical Industries , Egypt .

### Animals:

Twelve healthy male adult Baladi goats weighed  $45 \pm 5$  kg body and confirmed to be healthy by physical examination. Goats were fed a diet of barely grain and green feed in hygienic place for two months prior to the start of the experiment without any medications. The Ethics Committee was approved during the animal study.

### Sampling, isolation and identification of bacterial strain:

Milk and intestinal swabs from goat farms suffering from diarrhoea, weight loss, and fever were grown on MacConkey agar and incubated for 24-48 hour at 37°C. *Escherichia coli* colony was Lactose fermenting (pink colonies) were performed on Gram's negative response testing as submitted to TSI (Triple Sugar Iron), citrate, urease, and oxidase testing.

*Salmonella typhimurium* colonies were identified as non-lactose fermenting colonies and tested for Gram's reaction. Colonies of Gram negative bacilli were subjected for xld agar, TSI, citrate, urease, and oxidase test. *Bacillus subtilis* (medium, whitish, convex, rod coloneis) were tested for Gram positive reaction and subjected for gelatin, aesculin, casein, H<sub>2</sub>S production, nitrate tests.

### Identification by vitek 2 compact system

Identification were performed to the manufacture's instruction (Biomeriux VITEK-2 Compact ref Manual – Ref-414532, BioMe'rieux 2006) at Bacteriological Department, Animal Health Research Institute,

Egypt. A sterile swab was used for transmission of supposed colonies of culture to 3.0 ml of sterile saline (aqueous 0.45% till 0.50% NaCl, PH 4.5-7.0). The turbidity was monitored to the equivalent of 0.5-0.63 McFarland turbidity with a VITEK2 Densi-Check (biomerieux, France). Gram negative cards were inoculated with microorganism suspension for each isolate. Card was recognised by forty seven biochemical tests. Full cassette comprising microorganism suspension located in a vacuum chamber station. Air is re-introduced keen on the station. The organism suspension was transferred into micro-channels in wells. Inoculated cards are passed by cutting off the transfer tube and seal card prior to filling into cartridge incubator. Cards were incubated for six hours at  $35.5 \pm 1.0$  °C. Reading was recorded every 15 min automatically during incubation cards. Final results were printed within 6-8 hours. Cards were allotted into waste container automatically.

#### Experimental design:

All goats were fasted for twelve hours, weighed and equally classified into four groups of three goats each:

-The first group was received a single dose of tildipirosin at 4 mg/kg body weight I/V through the left jugular vein.

The second group was administered a single dose of 10 mg/kg body weight of triclabendazole orally one hour before I/V injection of tildipirosin in a dose of 4 mg/kg body weight according to **Abo El-Sooud (2003)**.

The third group was injected with a single dose of tildipirosin at 4 mg/kg body weight I/M into the left gluteal muscle.

The fourth group was administered a single dose of 10 mg/kg body weight of triclabendazole orally one hour before I/M injection of tildipirosin in a dose of 4 mg/kg body weight.

#### Sampling:

Blood samples from a jugular vein of all groups were collected at 5, 10, 30 minutes and 1, 2, 4, 6, 8, 12 and 24 hours after drug administration then left 30 minutes to clot.

Samples centrifuged at 3000 rpm for 15 minutes to get serum and retained at  $-20^{\circ}\text{C}$  till assayed.

#### Antimicrobial activity of antibiotics:

Antimicrobial activities of tildipirosin against *Bacillus subtilis*, *E.coli* (O78) and *Salmonella typhimurium* were assessed via agar well diffusion method. 0.1 ml of diluted inoculum was swabbed on Mueller Hinton plates. Wells (6mm diameter) were cut into the agar and 100  $\mu\text{L}$  of different concentrations of antibacterial agents ranging from 50 to  $0.09\mu\text{g/ml}$  are used. Activity was measured as inhibition zone in millimetres around the well (**Balouiri et al. 2016**) as recorded in Table 1.

#### Drug bioassay:

Serum tildipirosin concentrations detected by microbiological assay using *Bacillus subtilis* as a choice organism. Standard curve remained linear above the range of 0.39 -100  $\mu\text{g/ml}$ , minimal detectable limit was 0.39  $\mu\text{g/ml}$  (**Arret et al. 1971**).

#### Pharmacokinetic and statistical analysis:

The serum tildipirosin concentration time profile of each animal following intravenous and intramuscular administration was used to determine the pharmacokinetic variables using PK Solver (An add-in program for Micro-soft Excel, version 2). The data generated were exposed to statistical investigation using the Student's t-test with P.  $P < 0.05$  was significant level (**Snedecor and Cochran 1967 and Zhang et al. 2010**).

#### RESULTS

In vitro, tildipirosin was effective in the range of 50 to  $0.09\mu\text{g/ml}$  against *Bacillus subtilis* with zone of inhibition ranged between 30 to 10 mm while MIC of tildipirosin was  $3.125\mu\text{g/ml}$  against *Salmonella typhimurium* and  $25\mu\text{g/ml}$  against *E.coli*. From that *Bacillus subtilis* appeared to be the more sensitive organism so used in drug bioassay as shown in table (1).

Table (1): Antibacterial activity (zone of inhibition) of tildipirosin against *Bacillus subtilis*, *E. coli* and *Salmonella typhimurium* by agar well diffusion method

Drug conc. ( $\mu\text{g/ml}$ )	Diameter of zone of inhibition ( mm)		
	<i>Bacillus subtilis</i>	<i>E.coli</i>	<i>Salmonella typhimurium</i>
50	30	13	24
25	27	11	21
12.5	25	ND	17
6.25	23	ND	14
3.125	21	ND	11
1.563	19	ND	ND
0.781	16	ND	ND
0.390	14	ND	ND
0.195	12	ND	ND
0.09	10	ND	ND

ND: Non Detected

Semi-logarithmic plot of serum tildipirosin concentration-time data after intravenous injection alone or in combination triclabendazole indicated a two-compartment system of pharmacokinetics in goats. Tildipirosin was identi-

fied up to 24 h after I/V dosing in both groups. Serum tildipirosin concentration was declined in second group than first group (0.14 and 0.13 $\mu\text{g/ml}$ ) as shown in Figure 1.

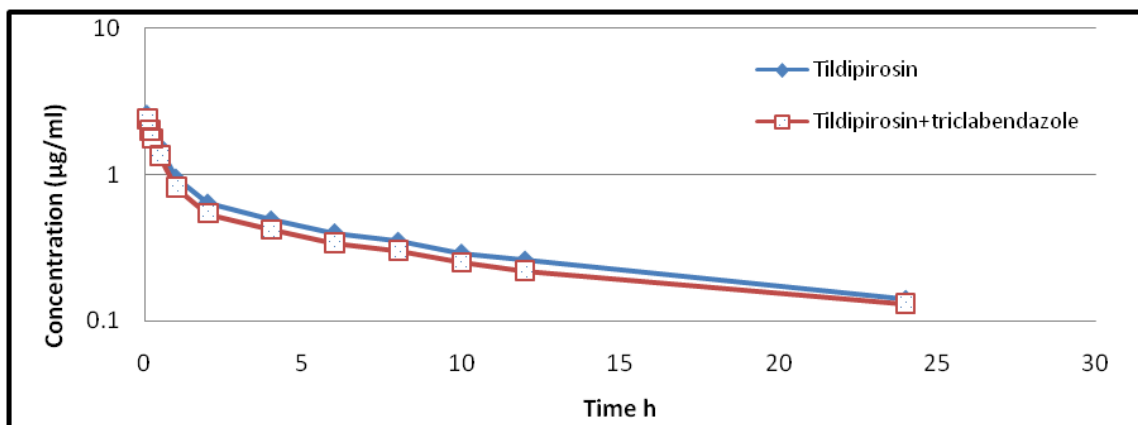


Fig.1. Semilogarithmic graph of the mean ( $\pm\text{SE}$ ) serum tildipirosin of first (tildipirosin) and second (tildipirosin+ triclabendazole) goat groups

After IV administration, the serum tildipirosin concentration at zero time ( $C_0$ ) showed lower in the second group ( $2.73 \pm 0.06\mu\text{g/ml}$ ) than those of the first group ( $2.82 \pm 0.04\mu\text{g/ml}$ ). The administration of triclabendazole had the ability to significant increase of distribution rate constant ( $\alpha$ ) and supported by high value of first order elimination rate constant

obtained from central compartment ( $k_{10}$ ), first-order rate constants for tildipirosin distribution between the central and peripheral compartments ( $K_{12}$  and  $K_{21}$ ). Apparent volume of peripheral compartment ( $V_2$ ), total body clearance ( $CL$ ), volume of distribution at steady state ( $V_{dss}$ ) and inter-compartmental clearances ( $CL_2$ ) were elevated in the second group

compared with first group. On the other hand, triclabendazole has the potential to reduce half-life of distribution and elimination ( $t_{1/2}$  Alpha and  $t_{1/2}$  Beta), the area under the curve (AUC0-

t), the area under the curve from zero to infinity and mean residence time in the second group as illustrated in table 2.

Table (2) Pharmacokinetic parameters of tildipirosin following a single intravenous dose (4 mg/kg b wt.) alone or with triclabendazole (10 mg/kg b.wt. orally) in goats (Mean  $\pm$  SD)

Parameter	Unite	First group (Tildipirosin )	Second group (Tildipirosin + triclabendazole)
C0	$\mu\text{g/ml}$	$2.82 \pm 0.04$	$2.73 \pm 0.06$
A	$\mu\text{g/ml}$	$2.18 \pm 0.01$	$2.13 \pm 0.06$
Alpha	$\text{h}^{-1}$	$1.72 \pm 0.14$	$1.88 \pm 0.02^*$
B	$\mu\text{g/ml}$	$0.63 \pm 0.02$	$0.59 \pm 0.01$
Beta	$\text{h}^{-1}$	$0.06 \pm 0.01$	$0.07 \pm 0.01$
k10	$\text{h}^{-1}$	$0.26 \pm 0.02$	$0.31 \pm 0.02^*$
k12	$\text{h}^{-1}$	$1.07 \pm 0.08$	$1.11 \pm 0.01^*$
k21	$\text{h}^{-1}$	$0.44 \pm 0.04$	$0.51 \pm 0.02$
t1/2 Alpha	h	$0.40 \pm 0.03$	$0.33 \pm 0.01^*$
t1/2 Beta	h	$9.88 \pm 0.87$	$7.79 \pm 0.47^*$
V	(mg)/( $\mu\text{g/ml}$ )	$1.41 \pm 0.02$	$1.45 \pm 0.04$
V2	(mg)/( $\mu\text{g/ml}$ )	$3.24 \pm 0.13$	$3.77 \pm 0.14^*$
V <sub>dss</sub>	mg/( $\mu\text{g/ml}$ )	$4.83 \pm 0.15$	$5.23 \pm 0.07^*$
CL	(mg)/( $\mu\text{g/ml}$ )/h	$0.38 \pm 0.02$	$0.45 \pm 0.02^*$
CL2	(mg)/( $\mu\text{g/ml}$ )/h	$1.51 \pm 0.09$	$1.91 \pm 0.05^*$
AUC 0-t	$\mu\text{g.h/ml}$	$8.68 \pm 0.24$	$7.56 \pm 0.30^*$
AUC 0-inf	$\mu\text{g.h/ml}$	$10.38 \pm 0.57$	$8.78 \pm 0.47^*$
AUMC	$\mu\text{g.h}^2/\text{ml}$	$131.14 \pm 18.38$	$101.28 \pm 10.6^*$
MRT	h	$12.58 \pm 1.08$	$11.50 \pm 0.61^*$

**C0**: "serum drug concentration at  $t=0$ ", **A**: "zero time intercept of the distribution phase", **Alpha**: "distribution rate constant", **B**: "zero time intercept of the elimination phase", **Beta**: "Elimination rate constant", **k10**: "first-order elimination rate constant from central compartment", **K12** and **K21**: "first-order rate constants for drug distribution between the central and peripheral compartments", **t<sub>1/2</sub>Alpha**: "distribution half-life", **t<sub>1/2</sub>Beta**: "elimination half- life"; **V**: "The apparent volume of central compartment", **V2**: "The apparent volume of peripheral compartment", **V<sub>dss</sub>**: "volume of distribution at steady state"; **CL**: total body clearance; **CL2**: "inter-compartmental clearances", **AUC0-t**: "area under the curve", **AUC 0-inf**: "area under the curve from zero to infinity", **AUMC**: " area under the first moment curve", **MRT**: "mean residence time".

Data presented as Mean  $\pm$  SD (P<0.05)

Following intramuscular injection, tildipirosin was detected post dose up to 24 h (0.15 and

0.12 $\mu\text{g/ml}$ ) in third and fourth groups respectively as illustrated in figure 2.

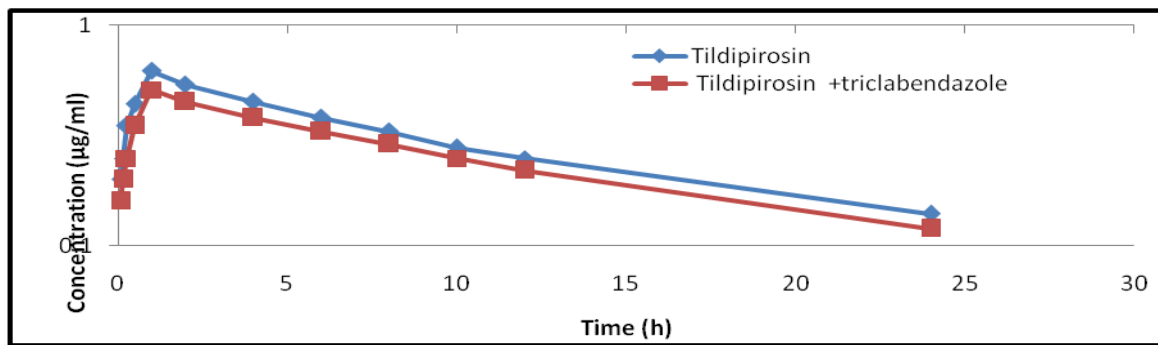


Fig 2. Semilogarithmic graph of the mean ( $\pm$ SE) serum tildipirosin in third (tildipirosin) and fourth (tildipirosin+ tricloabenzazole) goat groups

There was a substantial increase in both distribution and elimination rate constants ( $\alpha$  &  $\beta$ ) in third group contrary in fourth group, indicating a slower drop in serum tildipirosin concentrations. The values of time to peak concentration were  $1.14 \pm 0.02$  and  $1.23 \pm 0.02$ h in the third and fourth groups, respectively. Mean residence time (MRT) was significantly higher in third group ( $22.46 \pm 3.83$ h) than fourth group ( $18.64 \pm 1.69$ h) and that was supported by longer elimination half-life ( $17.71 \pm 3.12$ h)

The shorter absorption half-life ( $t_{1/2ab}$ ) in fourth group than third group indicated rapid absorption from the injection site.

The values of AUC<sub>0-t</sub>, AUC<sub>0-inf</sub> and AUMC and MRT in the fourth group were declined supported by shorter elimination half-life compared to the values of third group as illustrated in table 3.

Table (3) Pharmacokinetic parameters of tildipirosin following a single intramuscular dose (4 mg/kg b.w.) alone or with tricloabenzazole (10 mg/kg b.w. orally) in goats (Mean  $\pm$  SD)

Parameter	Unite	Third group (Tildipirosin)	Fourth group (Tildipirosin + tricloabenzazole)
A	$\mu$ g/ml	$0.36 \pm 0.05$	$0.21 \pm 0.03^*$
Alpha	$h^{-1}$	$0.20 \pm 0.01$	$0.43 \pm 0.01^*$
B	$\mu$ g/ml	$0.33 \pm 0.03$	$0.31 \pm 0.02^*$
Beta	$h^{-1}$	$0.03 \pm 0.01$	$0.04 \pm 0.01^*$
$K_{ab}$	$h^{-1}$	$2.89 \pm 0.02$	$2.94 \pm 0.03$
$k_{10}$	$h^{-1}$	$0.06 \pm 0.01$	$0.06 \pm 0.02$
$k_{12}$	$h^{-1}$	$0.05 \pm 0.02$	$0.04 \pm 0.03$
$k_{21}$	1/h	$0.15 \pm 0.01$	$0.08 \pm 0.05^*$
$t_{1/2\text{Alpha}}$	h	$3.43 \pm 0.3$	$1.63 \pm 0.41^*$
$t_{1/2\text{Beta}}$	h	$17.71 \pm 3.12$	$13.22 \pm 1.25^*$
$t_{1/2ab}$	h	$0.23 \pm 0.01$	$0.20 \pm 0.02^*$
C max	$\mu$ g/ml	$0.82 \pm 0.01$	$0.68 \pm 0.01^*$
T max	h	$1.14 \pm 0.02$	$1.23 \pm 0.02^*$
AUC 0-t	$\mu$ g.h/ml	$6.79 \pm 0.09$	$5.95 \pm 0.15^*$
AUC 0-inf	$\mu$ g.h/ml	$10.17 \pm 0.85$	$8.23 \pm 0.56^*$
AUMC	$\mu$ g.h <sup>2</sup> /ml	$230.83 \pm 56.81$	$154.21 \pm 24.40^*$
MRT	h	$22.46 \pm 3.83$	$18.64 \pm 1.69^*$

**A**: "zero time intercept of the distribution phase", **Alpha**: "distribution rate constant", **B**: "zero time intercept of the elimination phase", **Beta**: "Elimination rate constant",  $k_{ab}$ : "absorption rate constant", **k<sub>10</sub>**: "first-order elimination rate constant from central compartment", **K<sub>12</sub>** and **K<sub>21</sub>**: "first-order rate constants for drug distribution between the central and peripheral compartments",  **$t_{1/2\text{Alpha}}$** : "distribution half-life",  **$t_{1/2\text{Beta}}$** : "elimination half-life";  **$t_{1/2ab}$** : "absorption half-life"; **C<sub>max</sub>**: "peak drug concentration"; **T<sub>max</sub>**: "time to peak concentration"; **AUC 0-t**: "area under the curve", **AUC 0-inf**: "area under the curve from zero to infinity", **AUMC**: "the area under the first moment curve, **MRT**: "mean residence time".

Data presented as Mean  $\pm$  SD ( $P < 0.05$ )

## DISCUSSION

It is recognized that co-administration of binary drugs could affect the pharmacokinetics of both agents (**Benet and Sheiner 1985**). Pharmacokinetic communications between anthelmintic and antimicrobial drugs in veterinary medicine in case of *Fasciola* parasite and respiratory disease have deficiency researches given their frequent clinical use in combination.

Evaluation semi-logarithmic plot of serum tildipirson concentration-time data following its administration intravenously alone or with triclabendazole is used a two compartment open model. This behaviour associated with previously recorded by **Lei et al. (2018)** and **Galecio et al. (2020)**.

Serum tildipirson concentrations following intravenous and intramuscular administration in goats post oral dose of triclabendazole were declined than data of goats given only tildipirson. Oral triclabendazole was rapidly converted to its sulphoxide and sulphone derivatives in normal goats. The maximal plasma concentrations of sulphoxide and sulphone were comparable, ranging from 9 to 19 Hg/ml, and were reached an average of 12.8 and 25.6 hours after delivery, respectively. Both metabolites were removed slowly from plasma, with sulphoxide elimination half-lives of 22.4 h and sulphone elimination half-lives of 19.4 h. Triclabendazole sulphone and sulphoxide were identified in plasma 2 hours after triclabendazole injection (**Kinab and Bogan 1988**).

These findings were supported by **Abo El-Sooud (2003)** and **Atef et al. (2010)** who found that albendazole could lower serum concentration of enrofloxacin and tylosin, respectively.

Co-administration of triclabendazole significantly shortened tildipirson distribution and elimination half-life ( $t_{1/2\alpha}$  and  $t_{1/2\beta}$ ) after intravenous dosing. A previous study of **Abo El-Sooud (2003)** directed that serum enrofloxacin elimination half-life is lowered by administration of albendazole to lactating goats.

Following intravenous administration, the volume of tildipirson distribution at steady state ( $V_{dss}$ ) was pointedly greater in goats given tildipirson with triclabendazole ( $5.23 \pm 0.07$  mg/ $\mu$ g/ml) indicated large extra vascular distribution of the drug.  $AUC_{0-t}$  and AUMC of tildipirson were significantly decreased in goats pretreated with triclabendazole ( $7.56 \pm 0.30$   $\mu$ g.h/ml and  $101.28 \pm 10.6$   $\mu$ g.h<sup>2</sup>/ml, respectively). The drug was highly cleared in goats pre-treated with triclabendazole as the value of CL was  $0.45 \pm 0.02$  mg /( $\mu$ g/ml)/h. The rapid clearance and higher volume of distribution could clarify the lower tildipirson concentration and  $AUC_{0-t}$  pretreated with triclabendazole in goats. This was in parallel with the results of **Atef et al. 2010** who reported lower  $AUC_{0-t}$  and AUMC of tylosin with albendazole group than tylosin group in lactating goats.

Following intramuscular dosing, tildipirson absorbed from the injection site as absorption half-life value ( $t_{ab}$ ) recorded  $0.23 \pm 0.01$  h while this value lowered by triclabendazole ( $0.20 \pm 0.02$  h). The distribution of tildipirson was significantly decreased in triclabendazole pretreated group as the value of  $t_{1/2\alpha}$  was  $1.63 \pm 0.41$  h. The results revealed that intramuscular tildipirson injection with triclabendazole resulted in quicker elimination, with a  $t_{1/2\beta}$  value of  $13.22 \pm 1.25$  h and a lower MRT ( $18.64 \pm 1.69$  h). This discrepancy might be attributable to the action of triclabendazole on liver microsomal enzymes. This is consistent with the findings of **Escobar-Garcia et al. (2001)** and **Bapiro et al. (2002)** who identified activation of cytochrome P(450) CYP1A1 and CYP1A2 enzyme by albendazole at the transcriptional level that may be clinically significant in the metabolism of other drugs encourages. According to **Abo El-Sooud (2003)**, the decline of florfenicol level pretreated with albendazole than other treatments in goats might be clarified by its influence of liver microsomal enzymes. A research on deer, cattle, sheep, and pigs found substantial increase in liver microsomal biotransformation of albendazole (**Velik et al. 2005**). Furthermore, Albendazole and benzimidazole were reported to strongly activate cytochrome P-450 enzymes in rats and pigs (**Asteinza et al. 2000**; **Baliharova et al.**

2004).

Tildipirosin had MIC<sub>50</sub> values of 0.5, 1, 2 and 2 g/mL against *P. multocida*, *H. parasuis*, *A. pleuropneumoniae*, and *Bordetella bronchiseptica*, respectively as recorded by EMA (2015). In our study, tildipirosin serum concentration at 24 h after intramuscular treatment was greater than MIC against the aforementioned bacterial pathogens in both groups (Tildipirosin and Tildipirosin plus triclabendazole), with values of 0.15 and 0.12 g/ml, respectively. That indicated triclabendazole did not effect on the duration of tildipirosin administration in goats by I/M route.

Our research concluded that triclabendazole causes major variations in disposition kinetic of tildipirosin that enhances the distribution and elimination rate of tildipirosin in goats.

There are no adjustments to the dose regimen for tildipirosin in concurrent therapy with triclabendazole being investigated in goats because of investigations shortage of disposition kinetics effects.

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