Pharmacokinetics of toltrazuril and its metabolites toltrazuril sulphoxide and toltrazuril sulphone in pregnant and non-pregnant goats

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Abstract

The pharmacokinetic characteristics of toltrazuril (TZR) and its metabolites toltrazuril sulphoxide (TZR.SO) and toltrazuril sulphone ($TZR.SO_2$) were assessed in non-pregnant and pregnant goats. Ten healthy Baladi female goats were allocated into two groups (n = 5 per group): non-pregnant goats (group 1) and pregnant goats at 2–3 months of gestation (group 2). Toltrazuril was administered once orally to all goats at 20 mg/kg. Plasma samples were collected at 0 (before TZR administration), 0.5, 1, 2, 4, 6, 8, 12, 16, 24, 48, 72 h and 5, 7, 9, 12, 16, 20, 24, 27, 30, and 35 days post therapy to measure the concentrations of TZR and its metabolites. In pregnant goats, the maximum plasma concentration (C_{max}), time to reach C_{max} (T_{max}), and the area under the plasma concentration-time curve from time zero to the last sample ($AUC_{0\text{-last}}$) of TZR were significantly higher ($P < 0.05$) compared to the non-pregnant ones, whereas the volume of distribution (Vz_F_obs) and clearance (Cl_F_obs) were significantly lower ($P < 0.05$) in pregnant goats. No significant differences were observed in the elimination half-life ($T_{1/2\lambda z}$), and mean residence time (MRT) between the two groups. In non-pregnant goats, TZR.SO and $TZR.SO_2$ could be detected in plasma until 12 and 30 days, respectively; whereas in pregnant goats, they were quantified up to 16 and 35 days, respectively. Conclusively, TZR was well absorbed and rapidly metabolized to TZR.SO and $TZR.SO_2$ after oral dosing in goats. Pregnancy caused significant alterations in some of the pharmacokinetic indicators of TZR and its metabolites in goats.

Triazines, toxoplasmosis, elimination half-life, volume of distribution, HPLC

Triazines are benzene-aceto-nitrile compounds that possess antiprotozoal activity. Toltrazuril (TZR), a triazinetrione derivative, is synthetized from triazine by trimerization of nitrile (Harder and Haberkorn 1989). It is currently employed in clinical practice as a therapy for many protozoal infestations, particularly coccidiosis, neosporosis, and toxoplasmosis in various animal species (Kul et al. 2013; Qian et al. 2015; Stock et al. 2018). In addition, TZR has several favourable biological effects, for instance anti-inflammatory, analgesic, antineoplastic, and anticonvulsant activities (Harder and Haberkorn 1989).

The pharmacokinetics of TZR have been described in multiple species including rabbits (Hu et al. 2010; Kim et al. 2010), broilers (Kim et al. 2013), calves (EMEA 2000), pigs (Lim et al. 2010), ewes (Al-Qadri et al. 2020), and horses (Tobin et al. 1997). In these animals, TZR was well absorbed following oral administration and showed long plasma half-lives. Further, this compound is immediately converted to transient intermediate metabolite, toltrazuril sulphoxide (TZR.SO) and then metabolized to toltrazuril sulphone ($TZR.SO_2$), which is more stable and possesses antiprotozoal activity like parent compound (Benoit et al. 1993; Mundt et al. 2007; Lim et al. 2010).

To the best of the authors' knowledge, no data exist concerning the pharmacokinetics of toltrazuril in goats, especially in pregnant ones. The physiological changes associated with gestation may affect the disposition of the administered drug (Jeffries et al. 1988;

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Loebstein et al. 1997). Therefore, the current study was performed with the objectives to explore the pharmacokinetic characteristics of TZR and its derivatives TZR. SO and TZR. SO_2 in pregnant and non-pregnant goats after oral administration using high-performance liquid chromatography (HPLC) detection assay.

Materials and Methods

Chemicals

Toltrazuril oral suspension (Baycox® 5%, Bayer Animal Health, KS, USA) was used in the animal experiment. The reference standards of TZR, TZR.SO, and TZR.SO_2 were provided by Sigma-Aldrich (St. Louis, MO, USA). The HPLC grade methanol, acetonitrile and ethyl acetate were procured from Fisher Scientific (Waltham, MA, USA). Milli-Q system (Waters Corp., Milford, MA) was utilized to purify water for HPLC analysis.

Animals and experimental design

The study was conducted using ten healthy Baladi female goats, 2–3 years old. They were obtained from a private farm in the Dakahlia Governorate, Egypt. The goats were allotted according to their pregnancy status to two groups with 5 goats each. The pregnancy status was identified using ultrasonography. The first group involved non-pregnant goats, while the second group included pregnant goats at a gestation period from 2 to 3 months. The animals were placed individually in indoor pens in the Shoha Hospital, Faculty of Veterinary Medicine, Mansoura University, Egypt. Throughout the study, they were supplied with commercial pelleted feed (Al-Mohandes Co., Tanta, Egypt) and grass hay free of any medication, and with free access to water. The commercial pelleted feed consisted of 40% wheat bran, 30% yellow corn, 24% cotton seed meal, 3% molasses, 2% limestone, and 1% sodium chloride. The animals were allowed to acclimate for 15 days before the commencing of the study. The health status of goats was evaluated through physical examination. All goats received a single oral dose of 20 mg/kg of toltrazuril (Al-Qadri et al. 2020). Then, the goats were observed daily during the study period for any potential adverse effects such as gastrointestinal disturbances or any changes in the vital signs including the pulse, temperature, and respiration. The study protocol was reviewed and accepted by the Research Ethics Committee of the Faculty of Veterinary Medicine, Mansoura University, Mansoura, Egypt (approval No. R/89).

Blood sampling

Blood samples of 2 ml each were obtained from all goats through jugular vein puncture at time 0 (before toltrazuril administration), 0.5, 1, 2, 4, 6, 8, 12, 16, 24, 48, 72 h and 5, 7, 9, 12, 16, 20, 24, 27, 30, and 35 days post toltrazuril administration. Blood was immediately transferred to heparinized tubes and centrifuged at 1257 × *g* for 10 min and harvested plasma was preserved at -70 °C until assayed.

Analysis of toltrazuril and its metabolites in plasma samples

Sample preparation

A stock solution of TZR, TZR.SO, and TZR.SO_2 pure standards in methanol was prepared at a concentration of 1 mg/ml. Then, this stock solution was diluted using blank goat plasma as a diluent to prepare standard solutions of TZR, TZR.SO, and TZR.SO_2 at concentrations of 0.05, 0.1, 0.25, 0.5, 2.5, 5, 25, 50, 100 µg/ml.

Preparation of plasma samples and standards for HPLC analysis was performed following a previously reported technique (Al-Qadri et al. 2020) with some modifications. In brief, 100 µl aliquot of the plasma samples were added to 1 ml ethyl acetate and vortexed for 1 min. Then, the mixture was centrifuged at 173 × *g* for 10 min. After centrifugation, the supernatant was transferred to another tube and evaporated to dryness. The residue was redissolved in 200 µl acetonitrile. The extracted sample (100 µl) was injected into the HPLC column.

Chromatographic conditions

The concentrations of TZR and its metabolites in plasma were quantified according to the method announced by Zhaoling et al. (2014), with few modifications. The HPLC Agilent Series 1200 quaternary gradient pump, Series 1200 autosampler, Series 1200 UV VIS detector adjusted at 243 nm, and HPLC 2D Chemstation software (Hewlett-Packard, Les Ulis, France) were utilized. A Phenomenex C18 column (5 µm, 250 mm × 4.6 mm) was used for chromatographic separations. The analytical assay utilized a binary-gradient mobile phase with water and acetonitrile as mobile phase A and B, respectively. The gradient time program was as follows: 0–5 min (A–B, 48: 52 v/v); 5.1–8 min (A-B, 30: 70 v/v); 8.1–12 min (A–B, 0: 100 v/v);12.1–15 min (A–B, 48: 52 v/v). The mobile phase was delivered at a rate of 0.8 ml/min. The retention times of TZR, TZR.SO, and TZR.SO_2 were 6.5, 3.5, and 4.4 min, respectively.

The validation of the HPLC method was carried out by assessing recovery, sensitivity, precision, and linearity (Table 1). A linear correlation ($R^2 > 0.99$) was detected in the standard curve of TZR in the range of 0.05–100 µg/ml. The lower limits of detection (LOD) and quantification (LOQ) of TZR were 0.02 and 0.05 µg/ml, respectively. The TZR.SO calibration curve was linear through the concentrations of 0.25–100 µg/ml. Moreover, linearity of the TZR.SO_2 calibration curve was observed in the range of 0.1–100 µg/ml. The LOD and LOQ were 0.08 and 0.25 µg/ml for TZR.SO, and 0.03 and 0.1 for TZR.SO_2.

Table 1. Validation indicators of the high-performance liquid chromatography (HPLC) assay utilized for determination of TZR, TZR.SO, and TZR.SO_2. Data for recovery are presented as mean ± SEM.

Analyte	Recovery (%)	Intra-day RSD (%)	Inter-day RSD (%)	LOD	LOQ
TZR	104.53 ± 6.07	3.34	3.46	0.02	0.05
TZR.SO	102.49 ± 2.07	4.30	4.80	0.08	0.25
TZR.SO_2	98.12 ± 2.08	5.01	5.35	0.03	0.1

TZR - toltrazuril; TZR.SO - toltrazuril sulphoxide; TZR.SO_2 - toltrazuril sulphone.
Intra-day relative standard deviation (RSD) and Inter-day RSD % for TZR, TZR.SO, and TZR.SO_2 (n = 6, 0.25 µg/ml).
Mean recovery % for TZR (using spiked concentrations in the range of 0.05–100 µg/ml in triplicate analysis.
Mean recovery % for TZR.SO (using spiked concentrations in the range of 0.25–100 µg/ml in triplicate analysis.
Mean recovery % for TZR.SO_2 (using spiked concentrations in the range of 0.1–100 µg/ml in triplicate analysis.

Pharmacokinetic analysis

Non-compartmental model (WinNonlin 8.3 software [Certara, USA]) was applied to determine the pharmacokinetic features of TZR and its metabolites in each goat as described in literature (Kim et al. 2010; Lim et al. 2010; Al-Qadri et al. 2020). The peak plasma concentration (C_{max}) and the time to C_{max} (T_{max}) were identified from the relationship between concentrations versus time. The linear-log trapezoidal approach was used to measure the area under the plasma concentration-time curve from time zero to the last sample ($AUC_{0\text{-last}}$). The elimination half-life ($T_{1/2\lambda z}$) was estimated by linear regression using the slope of the terminal data points of the semilogarthmic plasma concentration-time plots ($T_{1/2\lambda z} = 0.693/\lambda z$; where λz is the first order rate constant).

Statistical analysis

All data were presented as means ± SEM. The normal distribution of data was assessed utilizing Shapiro-Wilk test. Differences in the plasma concentrations of TZR, TZR.SO, and TZR. SO_2 between pregnant and non-pregnant goats were investigated employing the 2-way analysis of variance. Mean comparisons were conducted using Bonferroni test. The pharmacokinetic indicators of TZR and its metabolites from pregnant and non-pregnant goats were compared utilizing Wilcoxon's rank sum test. If $P < 0.05$, differences were regarded as significant. These calculations were undertaken using Prism 7.0 (Graph Pad, USA).

Results

During the study period, all goats were healthy, and no obvious side effects were manifested during or after TZR therapy. The mean plasma concentrations of TZR at different time points following a single oral administration at 20 mg/kg in non-pregnant and pregnant goats are exhibited on a semilogarithmic chart in Fig. 1. TZR plasma concentrations were higher than the LOQ (0.05 µg/ml) up to the collected time points 24 and 27 days in non-pregnant and pregnant goats, respectively. A significant increase ($P < 0.05$) in the concentrations of TZR was detected in pregnant goats compared to non-pregnant goats at 12, 16, 24, 48, 72 h, 5, 7, 9, and 12 days-post treatment.

Figure 2 shows semilogarithmic graphs of TZR.SO concentrations in non-pregnant and pregnant goats after oral administration of TZR at a single dose of 20 mg/kg. TZR.SO rapidly appeared in plasma and could be detected until 12 days post TZR administration to non-pregnant goats; whereas, in pregnant goats, it was quantified (> 0.25 µg/ml) up to 16 days. Moreover, plasma TZR.SO concentrations were significantly higher ($P < 0.05$) in pregnant goats compared to non-pregnant ones at 72 h, 5, and 7 days after TZR oral therapy.

The plasma concentration time plots of TZR.SO_2 after a single oral dose of TZR at 20 mg/kg to non-pregnant and pregnant goats are displayed in Fig. 3. No TZR.SO_2 concentration could be detected in plasma after 30 and 35 days of TZR medication in non-pregnant and pregnant goats, respectively. In the non-pregnant group, the concentrations of TZR.SO_2 were significantly lower ($P < 0.05$) than in the pregnant one at 9, 12, and 16 days post TZR treatment.

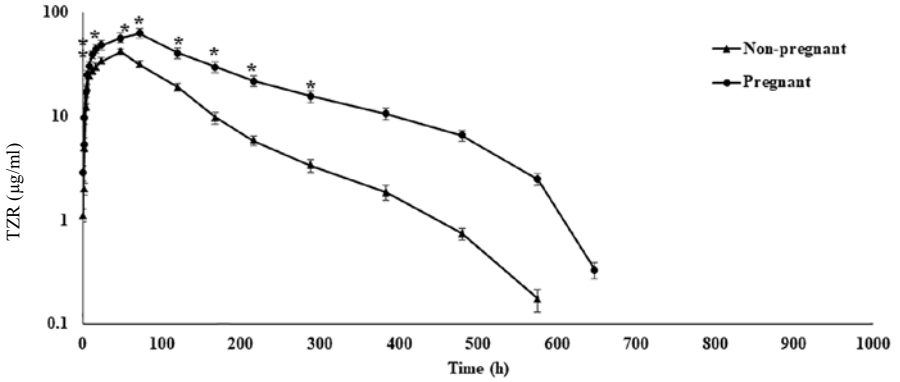

Fig. 1. Mean toltrazuril (TZR) plasma concentrations following a single oral administration in non-pregnant and pregnant goats at a dose of 20 mg/kg.
Values are shown as mean ± SEM (n = 5). *$P < 0.05$

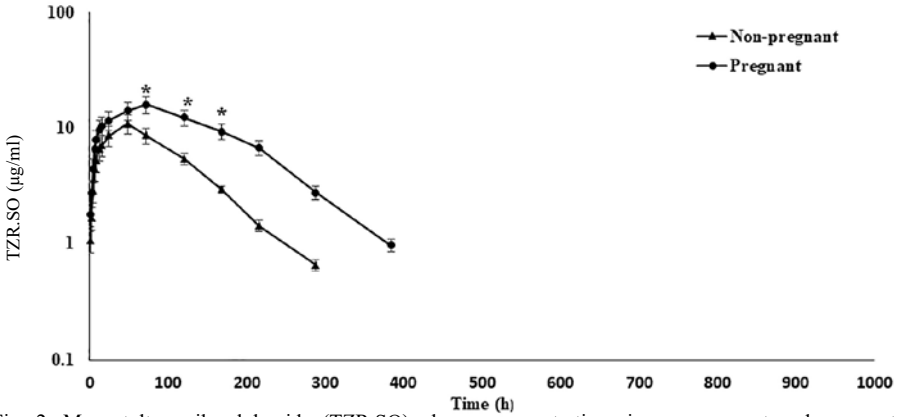

Fig. 2. Mean toltrazuril sulphoxide (TZR.SO) plasma concentrations in non-pregnant and pregnant goats following oral administration of toltrazuril (TZR) at a single dose of 20 mg/kg.
Values are expressed as mean ± SEM (n = 5). *$P < 0.05$

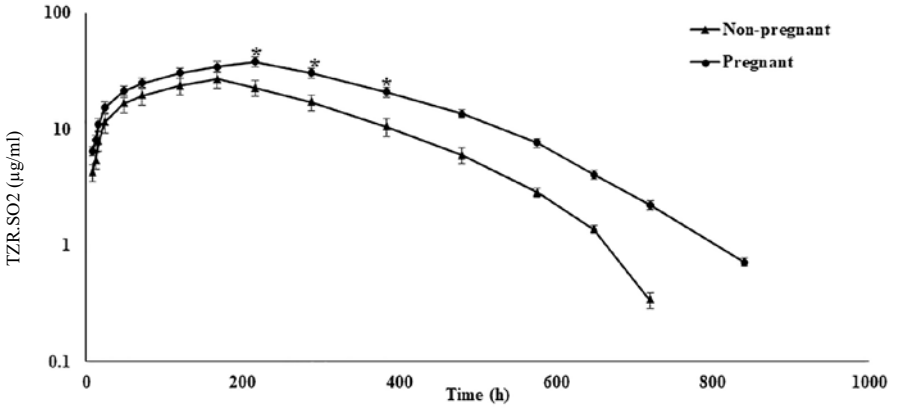

Fig. 3. Plasma concentration-time plots of toltrazuril sulphone (TZR.SO2) after administration of a single oral dose of toltrazuril (TZR) at 20 mg/kg in non-pregnant and pregnant goats.
Values are presented as mean ± SEM (n = 5). *$P < 0.05$

Table 2 elucidates the pharmacokinetic features of TZR in pregnant and non-pregnant goats following its oral administration once at 20 mg/kg. The values of $C_{max,}$ $T_{max,}$ and $AUC_{0\text{-last}}$ were significantly ($P < 0.05$) higher in pregnant goats compared to non-pregnant ones. Although $T_{1/2\lambda z}$ and the mean residence time (MRT) were longer in pregnant animals relative to the non-pregnant ones, this difference was not significant. In addition, in pregnant goats, the volume of distribution (Vz_F_obs) and clearance (Cl_F_obs) were significantly lower ($P < 0.05$) than in the non-pregnant ones.

Table 2. Pharmacokinetic indicators of TZR after its oral administration at a single dose (20 mg/kg BW) in non-pregnant and pregnant goats. Data are expressed as mean ± SEM (n = 5).

Indicator	TZR in non-pregnant goats	TZR in pregnant goats
C_{max} (µg/ml)	42.20 ± 2.56	63.12 ± 7.01*
T_{max} (h)	48.00 ± 0.00	72.00 ± 0.00*
λz (1/h)	0.011 ± 0.001	0.010 ± 0.002
$T_{1/2\,\lambda z}$ (h)	64.07 ± 3.58	70.04 ± 12.49
$AUC_{0\text{-last}}$ (µg*h/ml)	5401.33 ± 388.10	12908.48 ± 1480.85*
Vz_F_obs (ml/kg)	353.05 ± 43.09	161. 18 ± 32.92*
Cl_F_obs (ml/h/kg)	3.76 ± 0.27	1.62 ± 0.17*
MRT (h)	110.73 ± 3.72	170.97 ± 2.52

TZR - toltrazuril; C_{max} - peak plasma concentration; T_{max} - time to the highest plasma concentration; λz - the first order rate constant; $T_{1/2\,\lambda z}$ - elimination half-life; $AUC_{0\text{- last}}$ - area under the plasma concentration-time profile from 0 to last time; Vz_F_obs - volume of distribution scaled by bioavailability; Cl_F_obs - clearance divided by bioavailability; MRT - mean residence time; *$P < 0.05$

The pharmacokinetic indicators of TZR.SO in non-pregnant and pregnant goats after receiving TZR once orally at 20 mg/kg are summarized in Table 3. A significant increase ($P < 0.05$) in the values of T_{max} and $AUC_{0\text{-last}}$ of TZR.SO was seen in the pregnant group compared to the non-pregnant one. Meanwhile, a significant decrease ($P < 0.05$) in values of Vz_F_obs and Cl_F_obs was noticed in pregnant goats. There were no significant differences in C_{max}, $T_{1/2\lambda z}$, and MRT between the two groups.

Table 3. Pharmacokinetic indicators of TZR.SO after administration of a single oral dose of TZR (20 mg/kg BW) to non-pregnant and pregnant goats. Data are expressed as mean ± SEM (n = 5).

Indicator	TZR.SO in non-pregnant goats	TZR.SO in pregnant goats
C_{max} (µg/ml)	10.98 ± 2.07	16.02 ± 2.75
T_{max} (h)	48.00 ± 0.00	72.00 ± 0.00*
λz (1/h)	0.0127 ± 0.0009	0.0113 ± 0.0005
$T_{1/2\,\lambda z}$ (h)	55.66 ± 3.76	61.82 ± 2.88
$AUC_{0\text{-last}}$ (µg*h/ml)	1328.62 ± 166.33	2990.00 ± 479.52*
Vz_F_obs (ml/kg)	1249.36 ± 190.79	642.02 ± 101.60*
Cl_F_obs (ml/h/kg)	15.17 ± 1.47	7.20 ± 1.15*
MRT (h)	92.41 ± 5.67	129.52 ± 2.29

TZR - toltrazuril; TZR.SO - toltrazuril sulphoxide; C_{max} - peak plasma concentration; T_{max} - time to the highest plasma concentration; λz - the first order rate constant; $T_{1/2\,\lambda z}$ - elimination half-life; $AUC_{0\text{- last}}$ - area under the plasma concentration-time profile from 0 to last time; Vz_F_obs - volume of distribution scaled by bioavailability; Cl_F_obs - clearance divided by bioavailability; MRT - mean residence time; *$P < 0.05$

Table 4 illustrates the main pharmacokinetic indicators of TZR.SO_2 obtained after a single oral dose of 20 mg/kg TZR to non-pregnant and pregnant goats. Statistical comparison of theses indicators between both groups revealed no significant difference in the C_{max}, $T_{1/2\lambda z}$, MRT, and Vz_F_obs. Whereas, the differences in T_{max} and $AUC_{0\text{-}last}$ between the two groups were significant ($P < 0.05$) as their values increased in the pregnant group. Furthermore, the Cl_F_obs was significantly lower ($P < 0.05$) in pregnant goats compared to non-pregnant ones.

Table 4. Pharmacokinetic indicators of TZR.SO_2 after administration of a single oral dose of TZR (20 mg/kg BW) to non-pregnant and pregnant goats. Data are expressed as mean ± SEM (n = 5).

Parameters	TZR. SO_2 in non-pregnant goats	TZR. SO_2 in pregnant goats
C_{max} (µg/ml)	27.00 ± 4.35	38.10 ± 3.94
T_{max} (h)	168.00 ± 0.00	216.00 ± 0.00*
λz (1/h)	0.0119 ± 0.0020	0.00090 ± 0.0003
$T_{1/2\,\lambda z}$ (h)	73.13 ± 18.29	77.42 ± 2.82
$AUC_{0\text{-}last}$ (µg*h/ml)	8528.28 ± 1355.11	14257.44 ± 1359.38*
Vz_F_ obs (ml/kg)	252.07 ± 64.75	160.88 ± 13.89
Cl_F_obs (ml/h/kg)	2.58 ± 0.39	1.45 ± 0.14*
MRT (h)	236.74 ± 3.10	276.37 ± 3.53

TZR - toltrazuril; TZR.SO - toltrazuril sulphone; C_{max} - peak plasma concentration; T_{max} - time to the highest plasma concentration; λz - the first order rate constant; $T_{1/2\,\lambda z}$ - elimination half-life; $AUC_{0\text{-}last}$ - area under the plasma concentration-time profile from 0 to last time; Vz_F_obs - volume of distribution scaled by bioavailability; Cl_F_obs - clearance divided by bioavailability; MRT - mean residence time; *$P < 0.05$

Discussion

The present research was the first one to study the pharmacokinetics of TZR in goats. The investigation of the pharmacokinetic behaviour indicated that TZR was well absorbed after oral administration in goats. This finding is in accordance with the view of Dirikolu et al. (2009) who reported that triazine-based compounds are well absorbed following oral administration due to their lipophilic nature. The C_{max} of TZR in non-pregnant goats was 42.20 µg/ml, achieved at 48.00 h (T_{max}). This value was comparable to that reported for ewes and rabbits that received the same dose orally (20 mg/kg) (38.00 and 39.4 µg/ml, respectively) (Kim et al. 2010; Al-Qadri et al. 2020). On the contrary, it was higher than that found in piglets, pigs, and broiler chickens administered TZR at 20 mg/kg (7.50, 8.18, and 25.20 µg/ml, respectively) (EMEA 1999; Lim et al. 2010; Kim et al. 2013), calves that received TZR orally at 15 mg/kg (33.41 µg/ml) (EMEA 2000), and horses that were given TZR orally at 10 mg/kg (4.5 µg/ml) (Tobin et al. 1997). Furthermore, our results showed that the $T_{1/2\lambda z}$ of TZR in non-pregnant goats was 64.07 h. This $T_{1/2\lambda z}$ was nearly similar to that recorded in pigs (68.9 h, 20 mg/kg TZR, Lim et al. 2010). Lower values of $T_{1/2\lambda z}$ were observed following oral administration of TZR in rabbits and broilers (56.70 and 10.70 h, respectively) compared to those reported in our study (Kim et al. 2010, 2013). In contrast, the $T_{1/2\lambda z}$ found in calves and sheep (154.00 and 160.00 h, respectively; EMEA 2000; Al-Qadri et al. 2020) were higher than that reported in our study for non-pregnant goats, advocating that TZR is more rapidly eliminated in goats compared to sheep and calves. These discrepancies may be due to species and dose regimen variations.

After absorption from the gastrointestinal tract, TZR undergoes first-pass metabolism in the liver where it is rapidly transformed to an intermediary metabolite with a short half-life, TZR.SO, which is in turn oxidized to a more active derivative, TZR.SO_2. In the present

study, the T_{max} of TZR.SO was short (48.00 h) in non-pregnant goats that received TZR orally at 20 mg/kg. This finding points out the rapid conversion of the parent compound to TZR.SO. In contrast, a noticeable retardation of the C_{max} of TZR.SO_2 was recorded (the value of C_{max} was 27.00 µg/ml attained at 168.00 h [T_{max}]) which suggested that the oxidation of TZR.SO was slow. These results are in agreement with the EMEA report in piglets, which clarified that the T_{max} of TZR.SO and TZR.SO_2 were 48.00 and 168.00 h, respectively, after oral administration of TZR at 20 mg/kg (EMEA 1999).

Following oral administration of TZR to non-pregnant goats, the C_{max} of TZR.SO and TZR.SO_2 were 10.98 and 27.00 µg/ml, respectively. These values were consistent with the ones reported for rabbits (12.5 and 24.9 µg/ml, respectively; Kim et al. 2010). Nevertheless, the C_{max} of TZR.SO and TZR.SO_2 in goats were higher than those reported in sheep (5.8 and 7.00 µg/ml, respectively; Al-Qadri et al. 2020), pigs (4.01 and 8.74 µg/ml, respectively; Lim et al. 2010), and piglets (3.2 and 6.2 µg/ml, respectively; EMEA 1999) under the same conditions.

Moreover, in the current research, the goats had shorter $T_{1/2\lambda z}$ for TZR.SO and TZR.SO_2 (55.66 and 73.13 h, respectively) than those found in rabbits (68.8 and 82.3 h, respectively; Kim et al. 2010) which indicated that TZR metabolites were rapidly eliminated in goats compared to rabbits. The $T_{1/2\lambda z}$ of TZR.SO in non-pregnant goats was similar to that reported for pigs (53.20 h; Lim et al. 2010). However, the $T_{1/2\lambda z}$ of TZR.SO_2 in pigs (245.00 h) was longer than that reported for goats in this study.

The findings of this report demonstrated that the plasma TZR concentrations at all-post treatment time points were higher in pregnant goats compared to the non-pregnant ones. The elevated plasma TZR concentrations during pregnancy accounted for the increase in C_{max} (50%) and systemic availability (referred to as AUC; 139%). This may reflect an increase in the absorption of TZR from the gastrointestinal lumen in pregnant animals. The effect of pregnancy on the pharmacokinetics of TZR may be attributable to changes in the haemodynamics and body fluid volumes (Mitani et al. 1987; Perez et al. 2008). Our findings were in concordance with those of Al-Qadri et al. (2020) who reported an increase in TZR bioavailability in pregnant ewes compared to non-pregnant ones.

Furthermore, pregnant animals showed lower Cl_F_obs value for TZR than the non-pregnant ones. Similarly, Al-Qadri et al. (2020) recorded that the Cl_F_obs was significantly decreased in pregnant ewes. This is likely due to reduced hepatic blood flow and hepatic metabolism during pregnancy (Riggs et al. 1988).

In conclusion, oral administration of TZR in goats displayed favourable pharmacokinetic characteristics with rapid absorption, high systemic availability, and extensive distribution. Furthermore, alterations in some of the pharmacokinetic indicators were observed during pregnancy.

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Conflict of Interests

The authors declare no conflict of interests.

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