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Originall Article

Plasma pharmacokinetics of pioglitazone following oral or intravenous administration in Holstein cows

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ABSTRACT

Pioglitazone belongs to the thiazolidinedione (TZD) class of antidiabetic agents, with proven efficacy in increasing insulin sensitivity and in the treatment of type 2 diabetes mellitus in humans. Pioglitazone has been proposed as a potential feed additive to reduce insulin resistance and consequently some of the metabolic disorders in transition cows. This study was aimed at determining the pharmacokinetic parameters of pioglitazone following oral administration (PO) or intravenous (IV) injection. Six lactating Holstein cows were randomly assigned into two groups (n=3 cows per group) in a crossover design, and administered with pioglitazone (8 mg/kg BW) either per-oral (PO) or intravenously (IV), with an 8-day washout period. Blood samples were collected from the jugular vein before and up to 48 h after pioglitazone administration. Plasma pioglitazone concentration was determined by HPLC. The data were analyzed using a non-compartmental model for PO route, and a two-compartmental model for the IV route. The bioavailability of PO-administered pioglitazone was 58% and the highest plasma concentration (C_{max}), the time (t_{max}) at which the drug reached C_{max}, half-life ($t_{1/2}$), absorption rate constant (k_{ab}) and elimination rate constant (k_{el}) were 11.57±1.44 µg/mL, 5.67±0.07 h, 7.10±0.32 h, 0.28±0.09 h^{-1} and 0.10±0.013 h^{-1}, respectively. Elimination half-life ($t_{1/2\beta}$), volume distribution (V_{ss}) and elimination rate constant (k_{el}) after IV injection were 5.10±0.62 h, 0.12±0.01 L/kg and 0.47±0.06 h^{-1}, respectively. Because of the relatively high bioavailability and half-life, pioglitazone may be useful for oral administration as an insulin-sensitizing agent in dairy cows.

Keywords: Bioavailability, Pharmacokinetics, Pioglitazone insulin resistance, Dairy cow

INTRODUCTION

Insulin resistance during prepartum period in cows is an important adaptation that develops in skeletal muscle and adipose tissue, and continues into early lactation to direct nutrients toward the fetus and in support of lactation (Bell 1995). However, in prepartum cows, insulin resistance is followed by an increase in circulating concentrations of non-esterified fatty acids (NEFA) and consequently, a rapid decrease

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in dry matter intake (Allen *et al* 2005, Drackley 1999). High concentration of non-esterified fatty acids (NEFA) in transition cows is attributed to energy and immune related metabolic disorders, including displaced abomasum, ketosis, fatty liver, metritis and mastitis (Kaneene *et al* 1997). Several strategies have been used to decrease insulin resistance and attenuate metabolite disorders (Carlson 2005, Pescara *et al* 2010, Pires & Grummer 2007, Pires *et al* 2007, Spears *et al* 2012, Storlien *et al* 1991); however, a pharmacological method, based on administration of an exogenous ligand of peroxisome proliferator and activator receptor (PPAR) gamma, has been suggested as a newer approach for controlling prepartum insulin resistance in dairy cattle (Schmitt *et al* 2011, Schoenberg & Overton 2011, Smith *et al* 2007). The PPARs are members of the steroid hormone nuclear receptor family (Hammarstedt *et al* 2005). Like other nuclear receptors, upon activation by specific cognate ligands, PPARs work as transcription factors regulating expression of target genes. These receptors are widely distributed in the body, especially bovine adipose tissue (Sundvold *et al* 1997) as well as reproductive organs (Froment *et al* 2006). PPARγ has tremendous effects as differentiation regulator of adipocyte (Houseknecht *et al* 2002) influencing the capacity for fatty acid storage, and regulating several adipokines affecting insulin resistance (Knouff & Auwerx 2004). The PPARγ is activated by several endogenous (Berger & Moller 2002, Froment *et al* 2006, Knouff & Auwerx 2004, Moya-Camarena & Belury 1999) and exogenous ligands such as thiazolidinediones (TZDs). The TZDs are PPARγ agonists with antidiabetic effect, mainly through their actions in adipose tissues (Michalik *et al* 2006), reducing tumor necrosis factor-α (TNFα) expression, and decreasing leptin, free fatty acid (FFA) and triglyceride levels (Mudaliar & Henry 2001). There is evidence that TZD_S are able to reverse TNFα-induced insulin resistance (Kushibiki *et al* 2001) and improve adipose tissue differentiation, liver and muscle fatty acid oxidation and energy efficiency in beef cattle (Arévalo-Turrubiarte *et al* 2012). It is also known that administration of TZDs during late pregnancy increases dry matter intake (DMI), decreases NEFA, liver fat accumulation and body condition score (BCS) loss, and affects postpartum ovarian activity in dairy cows (Smith *et al* 2009, Smith *et al* 2007). Pioglitazone as a TZD, is a synthetic and specific ligand for PPARγ that is used for treatment of the type 2 diabetes mellitus (Ikeda *et al* 1990). By binding and activating PPARγ, pioglitazone affects plasma lipids, adipose tissue, and liver to reduce insulin resistance (Ikeda *et al* 1990, Mudaliar & Henry 2001). The pharmacokinetic parameter and bioavailability (F) of pioglitazone have been studied in human (Budde *et al* 2003, Eckland & Danhof 2000, Kalliokoski *et al* 2008) and non-ruminant animals (Umathe *et al* 2008, Wearn *et al* 2010). Pioglitazone bioavailability after oral administration to sheep was 62% (Ghoreishi *et al* 2012), 83% in humans (Eckland & Danhof 2000) and 50% in rats (Umathe *et al* 2008). The t_{max} of pioglitazone after oral administration in sheep was 6.4 h, while, it ranged between 1.5-3 h in other species (Budde *et al* 2003, Eckland & Danhof 2000, Fujita *et al* 2003, Kalliokoski *et al* 2008, Umathe *et al* 2008, Wearn *et al* 2010). Previous studies in human and horses showed a relatively long half-life (8-14 h) for pioglitazone after oral administration (Budde *et al* 2003, Eckland & Danhof 2000, Kalliokoski *et al* 2008). The half-life of pioglitazone in rats and sheep ranged between 2.5-4.5 h (Fujita *et al* 2003, Ghoreishi *et al* 2012, Umathe *et al* 2008). These values may not be applicable to ruminants because of differences in the gastrointestinal (GI) tract between ruminant and non-ruminant species. In ruminants, orally-administered drugs may be affected by ruminal microorganisms before absorption from the small intestine. Ghorieshi *et al* (2012) determined the pharmacokinetic of pioglitazone in sheep, but there are also differences in digestion processes between small and large ruminants. As TZDs are recently proposed for reducing insulin resistance and metabolic disorders in transition dairy cows, determination of their pharmacokinetic parameters is necessary for calculation of optimum oral doses. Therefore, the aim

of the present research was to study the bioavailability and some pharmacokinetic parameters of pioglitazone in dairy cows to determine an optimum dosage that may have the potential for use as a feed additive in transition cows.

MATERIALS AND METHODS

Animals. Six lactating Holstein cows with a mean (±SE) body weight of 564±22 kg (measured on the day before pioglitazone administration), 1.16±0.16 parities, and 15.63±0.70 kg milk yield were fed ad libitum with a basal TMR containing (DM basis) 1.48 Mcal/kg net energy for lactation and 16.80% crude protein. Prior to the start of the trial, an intravenous catheter was aseptically placed in the jugular vein.

Experimental design. Pioglitazone Hetero Drugs, India; Batch No: PHD 0510001 was administered intravenously or orally in a randomized crossover design. Cows were assigned into 2 groups (3 cows/group) based on the route of administration. Each cow received a single dose (8 mg/kg BW) orally or parentrally through the jugular vein. For IV injection, pioglitazone was dissolved (100 mg/mL) in propylene glycol (Merck, Germany). For oral administration, the same concentration of pioglitazone in water was administered via a drencher. There was an 8-day washout period between the two routes of administration with all cows receiving pioglitazone intravenously and orally. To omit any effect of propylene glycol, propylene glycol solution was also injected to the cows that received pioglitazone orally.

Blood sampling. Serial blood samples were collected through a catheter inserted into the jugular vein, using vacutainer tubes containing EDTA (10.5 mg, Monoject; Sherwood Medical) before, and at 0.08, 0.25, 0.5, 1, 1.5, 2, 4, 8, 12, 18, 24, 36 and 48 h after pioglitazone administration. Blood samples were centrifuged at 3000 g for 15 min at 4 °C and plasma samples were kept frozen at −20 °C until analysis.

Determination of plasma pioglitazone. Plasma levels of pioglitazone was determined by a validated high-performance liquid chromatography (HPLC) method with UV detection at a wavelength of 269 nm as described by Souri *et al* (2008). The mobile phase was prepared from acetonitrile and 140 mM KH_2PO_4 (40:60, v/v) at a final pH of 4.45, and the flow rate was set at 1.2 mL/min. Pioglitazone standard stock solution was prepared by dissolving pioglitazone hydrochloride in 100 mL methanol to obtain a final concentration of 200 µg/mL as the external standard. A series of pioglitazone standard solutions (0.5, 1, 10, 25, 50, 150 and 200 µg/mL) were prepared by subsequent dilution. Ethylparaben, dissolved in methanol (2 mg/mL), was used as the internal standard. The HPLC system consisted of the pumping (PLATINblue P-1 UHPLC, A60013, Knauer, Germany), detection (PLATINblue PDA-1, A62031), and separation (Eurospher 100-5-C18 column, 4 µm, 250 mm, 4.6 mm, Knaure, Germany) and PLATINblue AS-1autosampler units. An HPLC chromatogram of plasma sample spiked with the internal standard and pioglitazone is shown in Figure 1.

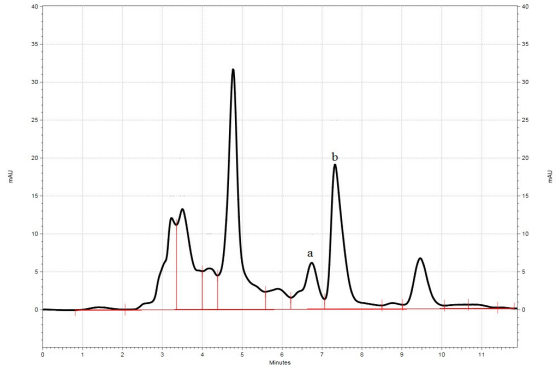

Figure 1. The HPLC chromatogram of plasma sample spiked with internal standard (peak a) and pioglitazone (50 ng/mL; peak b)

Pharmacokinetic analysis. Data were analyzed using WinNonlin professional software (version 5.2.1; Pharsight Corporation, CA, USA), and the F-test was used to identify the most compatible pharmacokinetic model. A non-compartmental pharmacokinetic analysis was performed to determine the pharmacokinetic parameters of pioglitazone by oral administration; however, the two-compartmental model was the best-fitted model for IV data. The pharmacokinetic

parameters determined in this study were: maximum plasma concentration (C_{max}), time at which maximum plasma concentration (t_{max}) was reached, distribution half-life ($t_{1/2\alpha}$), elimination half-life ($t_{1/2\beta}$), elimination rate constant (k_{el}), absorption rate constant (k_{ab}), mean residence time (MRT), and area under the first-moment time curve (AUMC). Bioavailability (F) of pioglitazone after oral administration was determined using the following equation:

$$(Dose_{IV} \times AUC_{oral}) / (Dose_{oral} \times AUC_{IV}) \times 100$$

In this equation, AUC_{oral} is the area under the curve for oral administration; AUC_{IV} is the area under the curve for IV administration; $Dose_{IV}$ and $Dose_{oral}$ are the pioglitazone dosages used for intravenous and oral administration routes, respectively.

RESULTS

The calibration curve of pioglitazone was linear ($R^2 \geq 0.99$). The intra-day and inter-day precisions of the method were less than 6% and 8%, respectively, and the limit of quantification was 40 ng/mL. Mean plasma concentrations and the graphic profile curve of mean plasma pioglitazone concentration vs. time after a single oral or IV administration of pioglitazone are shown in Table 1 and Figure 2, respectively.

Table 1. Plasma concentration (µg/mL) of pioglitazone [mean±SE; n=6] following a single intravenous injection (IV) and oral (PO) administration of pioglitazone (8 mg/kg BW) in Holstein cows.

Time (h)	IV	PO
0.08	144.13±3.99	0.57±0.11
0.25	113.72±6.02	2.39±0.23
0.5	105.61±7.10	3.00±0.24
1	86.21±4.36	3.41±0.19
1.5	47.12±2.11	4.39±0.24
2	29.13±1.22	5.04±0.34
4	18.71±1.08	6.65±0.52
8	11.31±0.98	9.52±0.51
12	8.02±0.55	10.27±0.39
18	3.89±0.38	6.36±0.37
24	1.32±0.20	3.10±0.20
36	0.35±0.06	0.92±0.11
48	0.04±0.01	0.27±0.06

Following a single oral administration of 8 mg/kg pioglitazone, the mean peak plasma concentration

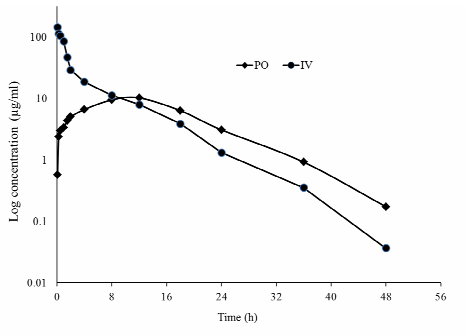

Figure 2. Semi-logarithmic plot of mean plasma concentration versus time after a single intravenous injection (IV, n=6) and oral administration (PO, n=6) of pioglitazone (8 mg/kg BW) in Holstein cows.

(C_{max}) was 11.57±1.44 µg/mL, and the time to reach maximum concentration (t_{max}) was 5.67±0.07 h (Table 2). The $t_{1/2\beta}$ of pioglitazone after oral administration was 7.10±0.32 h, and the mean values for k_{ab} and k_{el} were 0.28±0.09 (0.25 to 0.41) h^{-1} and 0.097±0.013 (0.07 to 0.011) h^{-1}, respectively. The volume of distribution (V_{ss}) was 0.39±0.09 (0.31 to 0.61) L/kg, while clearance (CL) and AUC were 0.038±0.005 (0.033 to 0.039) Lh^{-1}/kg and 215.33±26.00 (201.68 to 236.59) h^2 µg/mL, respectively.

Table 2. Pharmacokinetic parameters [mean±SEM; n=6] of pioglitazone following a single oral administration (8 mg/kg BW) in Holstein cows.

Pharmacokinetic parameters	Oral administration [a]
C_{max} (µg/mL)	11.57±1.44
t_{max}(h)	5.67±0.07
$t_{1/2\beta}$ (h)	7.10±0.32
k_{ab} (h^{-1})	0.28±0.09
k_{el} (h^{-1})	0.10±0.013
V_{ss} (L/kg)	0.39±0.09
CL (Lh^{-1} kg^{-1})	0.038±0.005
$AUC_{0-\infty}$ (h µg/mL)	215.33±26.00
F (%)	58.03±0.02

[a] Analyzed by non-compartmental approach. C_{max}, maximum plasma concentration; t_{max}, time to maximum plasma concentration; $t_{1/2\beta}$, elimination half-life; k_{ab}, rate of absorption constant; k_{el}, rate of elimination constant; V_{ss}, volume of distribution; $V1$, the central volume of distribution; CL, total body clearance; AUC, area under the plasma concentration time curve; AUMC, area under the first moment time curve; F, bioavailability.

The bioavailability of the orally-administered pioglitazone compared with IV injection was 0.58 ±0.02 (Table 2). The zero time intercept of distribution

(*A*) and elimination (*B*) phases following IV administration of pioglitazone were 138.00±23.00 and 37.02±5.37 µg/mL, respectively (Table 3). The $t_{1/2\alpha}$ and $t_{1/2\beta}$ were 0.50±0.07 and 5.10±0.62 h, respectively. The V_{ss}, volume of the central compartment (V_1) and volume of peripheral compartment (V_2) were 0.12±0.01, 0.05±0.006 and 0.074±0.001 L/kg in the plasma of IV received cows, respectively (Table 3). The values of other pharmacokinetic parameters in IV-administrated cows including k_{el}, distribution rate constant from central to peripheral compartment (K_{12}), and distribution rate constant from peripheral to central compartment (K_{21}) were 0.47±0.06, 0.68±0.23 and 0.41±0.09, respectively. Total clearance rate was 0.021±0.001Lh^{-1}/kg, and the area under the plasma concentration-time curve from time zero to infinity ($AUC_{0-\infty}$), MRT and AUMC were 371.00±24.00 h µg/mL, 5.61±0.27 h, and 2085±165 h^2µg/mL, respectively (Table 3).

DISCUSSION

This study was conducted to determine the bioavailability and several pharmacokinetic parameters of orally- and intravenously- administered pioglitazone for use as an agent in reducing insulin resistance and metabolic disorders in transition Holstein cows. The results showed a relatively high value for bioavailability (58%) and half-life (5.67 h) after oral administration. The elimination half-life ($t_{1/2\beta}$), volume of distribution (V_{ss}) and elimination rate constant (k_{el}) after IV injection were 5.10±0.62 h, 0.12±0.01 L/kg and 0.47±0.06 h^{-1}, respectively. Pioglitazone pharmacokinetics in sheep, as a small ruminant model, was studied by Ghoreishi et al. (2012). However, as far as we know there is no report on the bioavailability and pharmacokinetics of pioglitazone in cattle. The value of C_{max} obtained in the present study (11.57 µg/mL) was close to that found in sheep (10.2 µg/mL) and rats (13.6 µg/Ml) at an oral dose of 10 mg/kg (Fujita *et al* 2003, Ghoreishi *et al* 2012). However, oral administration of 1 and 5 mg/kg pioglitazone in horses (Wearn *et al* 2010) and rats (Singh & Patel 2013) produced a low peak plasma concentration (C_{max}) of 0.5 and 5.5 µg/ml, respectively.

Pharmacokinetic parameters	IV administration [b]
A (µg/mL)	138.00±23.00
α (h^{-1})	1.43±0.33
B (µg/mL)	37.02±5.37
β (h^{-1})	0.14±0.005
$t_{1/2\alpha}$ (h)	0.50±0.07
$t_{1/2\beta}$ (h)	5.10±0.62
k_{el} (h^{-1})	0.47±0.06
k_{12} (h^{-1})	0.68±0.23
k_{21} (h^{-1})	0.41±0.09
V_{ss} (L/kg)	0.12±0.01
V_1 (L/kg)	0.05±0.006
V_2 (L/kg)	0.074±0.001
CL (Lh^{-1} kg^{-1})	0.021±0.001
$AUC_{0-\infty}$ (h µg/mL)	371.00±24.00
MRT (h)	5.61±0.27
AUMC (h^2 µg/mL)	2085±165

Table 3. Pharmacokinetic parameters [mean±SEM; n=6] of pioglitazone following a single intravenous (IV) administration (8 mg/kg BW) in Holstein cows. [a] Analyzed by two-compartment body model. *A*, zero time intercept of distribution slope in the two compartment model; *B*, zero time intercept of elimination slope in the two compartment model; *α*, distribution rate constant; *β*, elimination rate constant; $t_{1/2\alpha}$, distribution half-life; $t_{1/2\beta}$, elimination half-life; k_{ab}, rate of absorption constant; k_{el}, rate of elimination constant; K_{12}, the distribution rate constants from central to peripheral compartment; K_{21}, distribution rate constants from peripheral to central compartment; V_{ss}, volume of distribution; *V*1, the central volume of distribution; *V*2, the peripheral volume of distribution; CL, total body clearance; AUC, area under the plasma concentration time curve; MRT, mean residence time; AUMC, area under the first moment time curve.

In human, at single oral doses between 15 to 45 mg, C_{max} ranged from 0.6 to 1.5 µg/mL (Carlson 2005, Pires *et al* 2007, Sundvold *et al* 1997). A linear change in pioglitazone C_{max} in the human (70 kg body weight) was recorded at oral doses between 0.03 to 0.86 mg/kg body weight (Eckland & Danhof 2000). Ghorieshi *et al* (2012) showed that oral administration of pioglitazone, 15- fold higher than that used in the human, produced a C_{max} in sheep which was seven times than in the human. However, we found that oral administration of pioglitazone at 8 mg/kg BW level, being 12-, 8- and 0.8- fold that used in human, horse and sheep, produced a C_{max} which was 8.3, 23 and 1.34 greater than that in human, horse and sheep, respectively (Budde *et al* 2003, Eckland & Danhof 2000, Ghoreishi *et al* 2012, Kalliokoski *et al* 2008, Wearn *et al* 2010).

The T_{max} of orally-administered pioglitazone in the human, rat and horse varied between 1.5 to 4 h (Budde *et al* 2003, Eckland & Danhof 2000, Kalliokoski *et al* 2008, Singh & Patel 2013). The t_{max} in the present study (5.67 vs. 6.4 h) was close to that in the sheep (Ghoreishi *et al* 2012). Such differences between the cow and non-ruminants may be attributed to differences in the anatomy and physiology of the digestive system. However, the shorter time to reach maximum concentration in the cow than in sheep might be related to the higher passage rate of digesta from the rumen to small intestine in dairy cows compared with the sheep. It is postulated that pioglitazone reaches the small intestine of the cow in a shorter time than in sheep. The mean absorption rate constant (k_{ab}) of pioglitazone after oral administration in the cow was higher than in the sheep (0.28 vs. 0.16 h^{-1}, respectively), which is consistent with the shorter time during which pioglitazone concentration reached its maximum level (C_{max}) in the cow. Consistent with our findings in the cow, Fujita *et al* (2003) reported a value of 0.38 h^{-1} for k_{ab} in rats receiving an oral administration of 10 mg/kg pioglitazone. Eckland and Danhof (2000) found a range of 0.4 to 1.2 h^{-1} in humans after an oral administration of 7.5 mg pioglitazone (approximately 0.11 h^{-1}, based on 70 kg BW). The half-life of pioglitazone after oral administration in the cow was close to that obtained in horses (Wearn *et al* 2010) and humans (Eckland & Danhof 2000) (7.10 vs. 9.2 and 9.9 h, respectively). However, the $t_{1/2\alpha}$ in the sheep (4.42 h; Ghoreishi *et al* 2012) and rat (2.5 to 3.82 h; Fujita *et al* 2003, Singh & Patel 2013, Umathe *et al* 2008) was smaller than in cows. The CL of pioglitazone found in the cow was close to that reported by Eckland and Danhof (2000) in humans, but it was smaller than that in rats (0.038 vs. 0.04 and 0.51 Lh^{-1} kg^{-1}, respectively). The CL in cows was 63% of that (0.038 vs. 0.06 Lh^{-1} kg^{-1}) in the sheep (Ghoreishi *et al* 2012). The smaller CL in the cow could be attributed to the longer half-life of the drug in this species. The rate of elimination constant in this study was slightly smaller than that in sheep (0.10 vs. 0.16 h); however, Fujita *et al* (2003) and Umathe *et al* (2008) reported larger k_{el} values in rats (0.26 and 0.22, respectively). The clearance rate of pioglitazone after a single IV injection in the cow was close to that in humans (Eckland & Danhof 2000) after 5 mg IV injection and assuming an average body weight of 70 kg (0.02 vs. 0.034, respectively). However, the level of clearance in cows was only 25% of that (0.02 vs. 0.08) obtained after an IV injection of 10 mg/kg BW pioglitazone in sheep (Ghoreishi *et al* 2012). According to Budde *et al* (2003), the hepatic extraction ratio of pioglitazone in human is low, however, it is affected by the dosage administered and the capacity of hepatic enzymes involved in catabolism of pioglitazone (Eckland & Danhof 2000). Although there are no data on the hepatic extraction ratio or capacity of hepatic enzymes, lower clearance of pioglitazone in the present study compared with the sheep may be due to differences in the capacity of hepatic enzymes involved in pioglitazone metabolism. Eckland and Danhof (2000) suggested that extensive binding of pioglitazone to plasma proteins ($\geq$ 97%) can lead to relatively low volume of distribution in humans (0.25 L/kg). The longer half-life in cows than in sheep (7.1 vs. 4.42 h) may be associated with a greater proportion of the drug bound to plasma proteins, leading to lower hepatic clearance. This is more plausible by comparison of the differences in volume distribution between cows and sheep (0.12 vs. 0.30 L/kg, respectively), where lower V_{ss} in cows probably indicates lower free fraction of the drug in plasma. The volume distribution for pioglitazone obtained in the present study after oral administration of 8 mg/kg pioglitazone was close to that in sheep (Ghoreishi *et al* 2012) and rats (Fujita *et al* 2003) using a dose of 10mg/kg (0.39 vs. 0.38 and 0.25, respectively). The bioavailability (F) of pioglitazone in the present study (58%) was close to values reported in sheep (62%), and rats (48-50%) receiving an oral dose of 10 mg/kg BW (Fujita *et al* 2003, Ghoreishi *et al* 2012, Umathe *et al* 2008), but much smaller than the 80% value in humans (Eckland & Danhof 2000). In conclusion, the long half-life of pioglitazone in the cow was higher than the

corresponding values in other species. The time interval to reach maximum concentration in plasma was also longer than in humans and rats. The bioavailability of pioglitazone was relatively high following oral administration, suggesting its potential for oral administration as an insulin-sensitizing agent in dairy cows.

Ethics

I hereby declare all ethical standards have been respected in preparation of the submitted article.

Conflict of Interest

The authors declare that they have no conflict of interest.

Acknowledgments

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