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Short communication

Simple HPLC method for determination of rosiglitazone in sheep plasma and amniotic fluid and its application in a pregnant sheep model

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ABSTRACT

This paper describes the development of a sensitive high performance liquid chromatography (HPLC) method for quantification of rosiglitazone in sheep plasma and amniotic fluid. Samples were prepared by liquid–liquid extraction using tert-butyl methyl ether, and rosiglitazone was quantitated by HPLC using a C18 column and fluorescence detector with an excitation wavelength of 247 nm and emission wavelength of 367 nm. The mobile phase consisted of ammonium acetate (10 mM, pH 5.2) and acetonitrile (56.5:43.5, v/v) with a flow rate of 1 ml/min. Ketoconazole was used as the internal standard (IS).

The plasma calibration curve was linear over the range of 2.5–250 ng/ml (mean $r^2 = 0.9940 \pm 0.0024$; $n = 6$) with accuracy of 99.4–102.8% over the calibration range. The intra-day and inter-day coefficient of variation (%CV, percent coefficient of variation) were in the range of 0.01–8.68% in sheep plasma. Similar performance was achieved for amniotic fluid. The described method was successfully applied to quantitate rosiglitazone concentrations in the pregnant ewe and her fetus.

1. Introduction

Rosiglitazone ($C_{18}H_{19}N_3O_3S$) 5-[[4-[2-(methyl-pyridin-2-ylamino)ethoxy]phenyl]methyl]-thiazolidine-2,4-dione (Fig. 1a) is a high affinity agonist for the transcription factor peroxisome proliferator-activated receptor-γ (PPAR-γ) which belongs to the thiazolidinedione (TZD) class of drugs. TZDs have been shown to improve insulin action *in vivo* and are widely used in the treatment of insulin resistance in conditions such as type 2 diabetes, obesity and polycystic ovary syndrome [1]. Treatment of diabetic patients with TZDs also reduces fasting and postprandial glucose levels and effectively lowers plasma insulin and triglyceride levels [2].

The increasing incidence of maternal overweight and obesity has contributed to a global increase in the number of pregnancies complicated by gestational diabetes or insulin resistance. Maternal diabetes, gestational diabetes or even mild impairments in maternal glucose tolerance all result in increased glucose concentrations in the fetus, and this is associated with an increased risk of obesity and type 2 diabetes in these infants later in life. As a result of the adverse consequences of being exposed to high glucose levels during development, it has been suggested that interventions to improve maternal insulin sensitivity during pregnancy could protect the fetus from these problems. Whilst TZDs are known to be effective in improving insulin sensitivity in adults, the use of TZDs is contraindicated during pregnancy largely due to an association with increased retardation of development and fetal deaths in rats and rabbits at high doses [3]. Limited evidence suggests that rosiglitazone crosses the placenta, but that this transfer is limited by active efflux of rosiglitazone via p-glycoprotein resulting a lower exposure of the fetus compared to the mother [4].

As in humans, the sheep accumulates significant fat stores *in utero* and the main organ systems develop along a similar trajectory to the human fetus [5]. The aim of this study was to determine the pharmacokinetics of rosiglitazone in the sheep fetus as part of a larger study aimed at investigating the effects of direct activation of PPAR-γ by rosiglitazone on fetal growth and organ development. A simple and reliable method which will enable the determination of rosiglitazone concentrations in plasma samples from the pregnant ewe and her fetus and in amniotic fluid is important for understanding how the concentrations of this drug in the fetus are influenced by placental transfer and to what extent the fetus has the ability to metabolize this drug.

Several methods for determination of rosiglitazone in human, dog and rodent biological fluids [6–10] have been published but there is no specific method for sheep plasma, and no method exists for quantifying concentrations in amniotic fluid. The low dose of rosiglitazone and small volume of sample available for study also required the development of a sensitive method to overcome these

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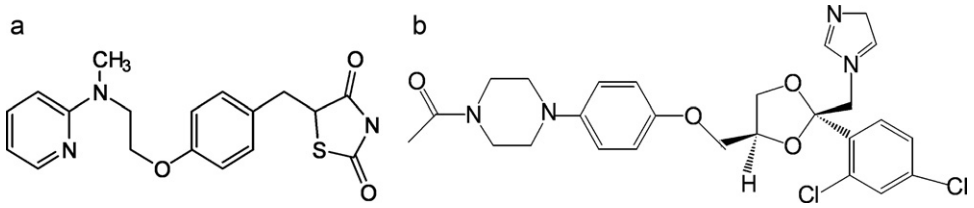

Fig. 1. Chemical structure of rosiglitazone (a) and ketoconazole (b) as internal standard.

limitations. Furthermore, previously published methods have limitations such as requiring access to liquid chromatography/mass spectrometry (LC/MS) [8], complicated sample preparation and the use of large sample and organic solvent volumes [9].

Therefore, the aim of this study was to develop a sensitive and specific assay that has a simple extraction method, and is suitable for small plasma and amniotic sample volumes. In this paper, we describe a novel HPLC method for the determination of rosiglitazone in sheep plasma and amniotic fluid and the application of this method to determine rosiglitazone concentrations in maternal and fetal sheep plasma and amniotic fluid after continuous infusion of rosiglitazone to the fetus.

2. Experimental

2.1. Chemical and reagents

Rosiglitazone was purchased from Cayman Chemical Company (MI, USA). Ketoconazole (internal standard) was purchased from Sigma–Aldrich (St. Louis, MO, USA), and tert-butyl methyl ether from Sigma–Aldrich Pty. Ltd (Seelze, Germany), acetonitrile was purchased from Scharlau Chemie S.A. La. Jota (Barcelona, Spain). Ammonium acetate was purchased from Fluka Chemi GmbH (Buchs, Switzerland). Milli-Q water was prepared using a Milli-Q Ultrapure Water System (Millipore, USA). Sheep plasma and amniotic fluid were collected and processed in house from drug free animals.

2.2. Chromatographic conditions

A Shimadzu (Japan) HPLC was equipped with a RF-10AxL fluorescence detector, SCL-10A System Controller, SIL-10A Auto Injector, LC-10AS pump and data integrator INTG-10CR5A.

The chromatographic separations were carried out at room temperature on a C18 Phenomenx column (GEMINI 5 μm 110 A°, Australia) which was fitted with a refillable guard cartridge pre-column (GEMINI, Australia).

The mobile phase consisted of (43.5:56.5, v/v) acetonitrile and 10 mM ammonium acetate buffer (pH 5.2) with a flow rate of 1 ml/min. The detection of peaks was performed by using the fluorescence detector set at excitation and emission wavelengths 247 nm and 367 nm, respectively [10].

2.3. Preparation of stock and working solutions

Rosiglitazone (stock solution) 1 mg/ml was dissolved in ethanol separately for standard curve and quality control solutions. The working solutions were prepared in appropriate concentrations in Milli-Q water. Ketoconazole as the internal standard (IS) stock solution was dissolved in ethanol (1.4 mg/ml) and working solution of 7 μg/ml was prepared in Milli-Q water.

2.4. Preparation of samples

Blank plasma (200 μl) was spiked with the appropriate stock solution of rosiglitazone to yield concentrations of 2.5, 5, 10, 25, 50, 100 and 250 ng/ml for standard curve calibration samples. Quality control samples were prepared by spiking blank plasma with rosiglitazone to obtain concentrations of 7.5 (LQC), 20 (MQC), and 100 (HQC) ng/ml and were analyzed in duplicate in each analytical run.

Twenty microliter of IS working solution was added to each sample, vortex mixed briefly (1–2 s), followed by the addition of 1 ml of tert-butyl methyl ether. The solution was vortexed for 40 s and centrifuged (4400 × g for 10 min). The supernatant was transferred to another clean test tube and dried under nitrogen gas at 40 °C. The residue was reconstituted with 200 μl of mobile phase and 20 μl of each sample was injected on to the HPLC system.

Sheep plasma and amniotic fluid samples were prepared as above after adding 20 μl of IS working solution.

2.5. Selectivity, stability and linearity

Selectivity and optimization of the chromatographic conditions were determined by preparing blank sheep plasma ($n = 6$) and comparing with the plasma samples spiked with a concentration of rosiglitazone at the lower limit of quantification (LLOQ) ($n = 12$). Blank mobile phase vials were inserted in random for assessing the rosiglitazone or IS carryover.

The stability of rosiglitazone was tested using 6 replicates of LQC, MQC and HQC samples for freeze–thaw, short-term stability and stability after sample preparation. The freeze–thaw samples underwent 3 cycles of freeze and thaw before preparing the samples for analysis, the short term stability samples were kept on the bench for 2 h before preparing the samples for analyzing, and post preparation samples were extracted and kept in mobile phase for 8 h in HPLC vials.

The range of the calibration curve was from 2.5 ng/ml to 250 ng/ml and consisted of seven standard concentrations in sheep plasma and amniotic fluid. Calibration curves in sheep plasma were analyzed daily for 6 days with the lower concentration (2.5 ng/ml) in 6 replicates for one run and calibration curves for amniotic fluid were analyzed daily for 3 days with the lower concentration (2.5 ng/ml) with 6 replicates for one run. For each calibration curve the rosiglitazone peak area to IS peak area ratio was calculated and plotted against nominal rosiglitazone concentrations. Linear regression analyses (GraphPad Prism v5.01, GraphPad Software, CA), weighted $1/y^2$, of peak area ratios against nominal concentrations of rosiglitazone provided an estimate of slope, intercept and coefficient of determination (r^2).

2.6. Accuracy and precision

Accuracy and precision were determined over 5 analytical runs with duplicate QC samples with concentrations of 7.5, 20, and 100 ng/ml, with one run consisting of 6 replicates of each QC sample which calibrated with the standard curves concomitantly prepared on the day of analyses. Accuracy was calculated as (calculated concentration/nominal concentration) × 100% for each individual sample. The overall mean accuracy at each concentration examined was taken as the mean accuracy. To estimate the inter-assay

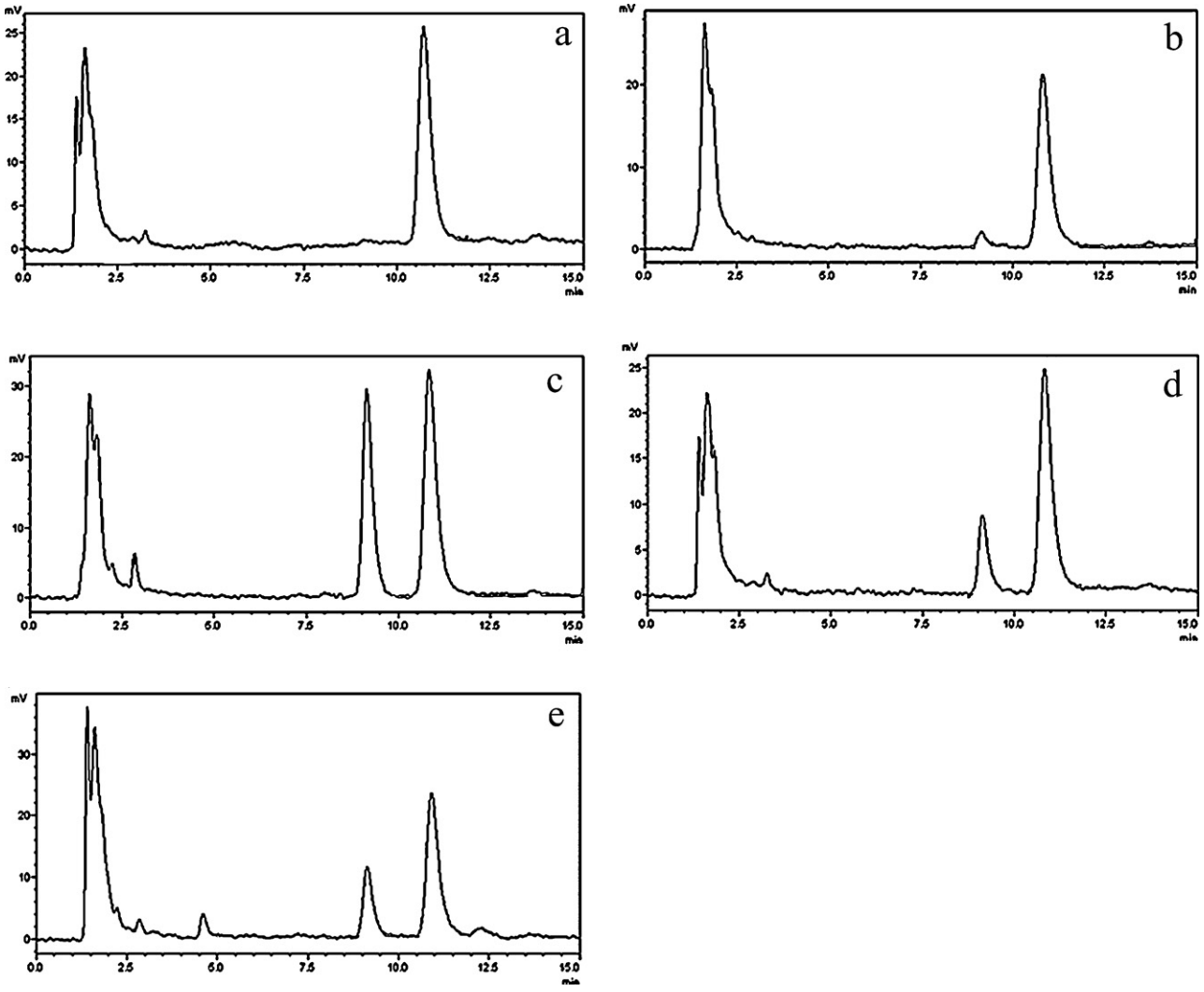

Fig. 2. Representative HPLC chromatograms of rosiglitazone and ketoconazole (IS) in sheep plasma. Plasma sample spiked with 700 ng/ml IS (a); plasma sample at 2.5 ng/ml (b); rosiglitazone 25 ng/ml with IS (c); fetal plasma (d) and maternal plasma (e) at day five after subcutaneous infusion of rosiglitazone to the fetus. The retention times for rosiglitazone and internal standard are approximately 9 and 11 min, respectively.

and intra-assay precision, a linear mixed-effects model approach with assay "day" as a random effect, using the analyses package "R" was employed [11]. This approach was employed to account for the unbalanced number of replicates across assay-days (duplicates for 5 days, and 6 replicates for the sixth assay day) and allowed for the accurate estimation of both intra-assay and inter-assay precision from our data without the underestimation of inter-assay precision estimates offered by alternative methods [11].

2.7. Extraction efficiency

Recovery of rosiglitazone at concentrations of 7.5, 20, and 100 ng/ml was determined by comparing of the peak area of rosiglitazone in the extracted QC samples ($n = 6$ for each QC) versus peak area of rosiglitazone of direct injection of equivalent concentrations of rosiglitazone diluted in the mobile phase ($n = 6$ for each equivalent concentration). Recovery of internal standard (IS) was determined by comparing the response obtained from extracted blank plasma spiked with 20 μl of working solution of IS versus the response obtained after direct injection of a similar concentration of IS diluted in the mobile phase.

2.8. Application of the method

Following the validation of the assay, rosiglitazone concentrations were determined in plasma samples from a pregnant ewe and her fetus. The study was approved by the Institute of Medical and Veterinary Sciences and University of Adelaide Animal Ethics Committee, Adelaide, Australia. Rosiglitazone 15 mg/ml (in 15% ethanol) was infused into the sheep fetus at a constant rate of 10 μl/h (equal to 3.6 mg/fetus/day) by subcutaneous implantation of 4 osmotic pumps (ALZET Osmotic Pumps, Durect Corporation, Cupertino, Canada) over the scapula of the fetus at between 123 and 126 days gestation (term, 150 days). The average duration of the infusion was 16 ± 1 days [5]. Blood was collected via maternal jugular vein and fetal carotid artery catheters and amniotic fluid was collected via an amniotic catheter each day for the first 5 days after surgery and then every 2 days until the end of the infusion. Blood was centrifuged at $1500 \times g$ for 10 min at 4 °C and plasma stored at −20 °C until analyses. The concentration of rosiglitazone in maternal and fetal plasma and amniotic fluid was determined by the described method and the fetal to maternal plasma concentration ratio (F:M) calculated for each time point.

Table 1
Intra-day and inter-day accuracy and reproducibility for determination of rosiglitazone ($n = 6$ assays). Extraction efficiency is presented as mean ± SD; coefficient of variation (CV%), LLOQ indicates lower limit of detection; LQC low quality control sample; MQC medium quality control sample; HQC high quality control sample.

	Mean accuracy (%)	Inter-assay precision (%CV)	Intra-assay precision (%CV)	Mean r^2 (±SD)	Mean slope (±SD)	Extraction efficiency (%)
Plasma				0.9940 ± 0.0024	0.001 ± 0.0003	
LLOQ (2.5 ng/ml)	101.1	1.41	6.4			
LQC (7.5 ng/ml)	101	6.47	5.3			87.78 ± 9.88
MQC (20 ng/ml)	99.38	0.01	8.68			92.49 ± 7.50
HQC (100 ng/ml)	102.81	0.01	6.41			86.63 ± 7.46
Amniotic fluid				0.9970 ± 0.0036	0.0012 ± 0.00001	
LLOQ (2.5 ng/ml)	99.40	1.20	0.70			
LQC (7.5 ng/ml)	94.60	0.00	10.40			85.40 ± 7.34
MQC (20 ng/ml)	95.30	10.60	5.20			92.64 ± 4.82
HQC (100 ng/ml)	107.80	0.00	12.20			105.06 ± 4.40

3. Results

3.1. Selectivity, stability and linearity

Representative chromatographs of blank sheep plasma, blank plasma spiked with IS and blank plasma spiked with rosiglitazone 2.5 ng/ml are shown in Fig. 2. The retention times for rosiglitazone and IS were approximately 9 and 11 min, respectively. There were no endogenous plasma interfering peaks with rosiglitazone or IS. The stability of rosiglitazone has been shown by previous studies [10] and this was confirmed in our study. Rosiglitazone was stable over 2 h at room temperature (99.4 ± 4.7% for the mean of all QC samples, $N = 6$ for each of the 3 QC levels) and 8 h in the mobile phase after being extracted (101.3 ± 1.9% for the mean of all QC samples, $N = 6$ for each of the 3 QC levels). Rosiglitazone was also stable after three freeze–thaw cycles (90.5 ± 9.3% for the mean of all QC samples, $N = 6$ for each of the 3 QC levels).

The calibration curve was linear over the range of 2.5–250 ng/ml in sheep plasma. The mean ± SD regression coefficient (r^2) was 0.9940 ± 0.0024 ($n = 6$ runs) in plasma and 0.997 ± 0.0036 in amniotic fluid ($n = 3$ runs). LLOQ was 2.5 ng/ml and was at a signal to noise ratio of 10. The mean of coefficient of determination (r^2) and the mean of intercept for 6 standard curve runs are presented in Table 1.

3.2. Accuracy, precision and recovery

The assay demonstrated excellent precision and accuracy over the entire calibration range, both within and between days. Table 1 shows the precision and accuracy of the method for quality control samples both intra-assay and inter-assay. The precision of the developed method (CV%) was 6.5% and 8.7% for inter-assay and intra-assay, respectively. The mean accuracy of the developed method was between 99.4% and 102.8%. The recovery of rosiglitazone is shown in Table 1 and recovery of IS was 90%.

3.3. Application of the method

The concentration of rosiglitazone in plasma from the ewe and fetus and in amniotic fluid after constant infusion of rosiglitazone with the dose of 15 μg/h (equal to 3.6 mg/fetus/day) were quantified by the described method. Fig. 3 shows the concentration-time profile of rosiglitazone in both maternal and fetal sheep plasma over days 1–15 of constant subcutaneous infusion of rosiglitazone to the fetus. The amniotic fluid of the fetus was evaluated; however there was no peak of rosiglitazone in the amniotic fluid. The ratio of fetal to maternal plasma concentration of rosiglitazone is illustrated in Fig. 4.

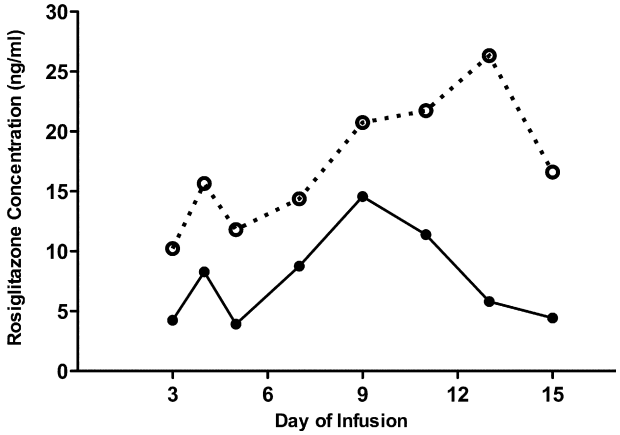

Fig. 3. The concentration time profile of rosiglitazone for a pregnant ewe and her fetus during constant subcutaneous infusion of 15 μg/h rosiglitazone to the fetus.

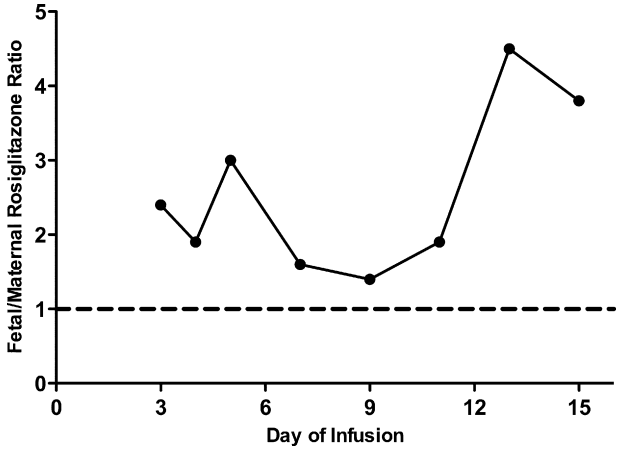

Fig. 4. The fetal to maternal ratio of rosiglitazone concentration during constant subcutaneous infusion of 15 μg/h rosiglitazone to the fetus. Dashed line indicates an F/M ratio of 1.

4. Discussion

Using fluorescence detection, a fast, robust and reliable HPLC method was developed for detection of rosiglitazone in sheep plasma. The use of a very small amount of plasma (200 μl) and a low LLOQ which is necessary for detecting small amounts of rosiglitazone in plasma after administration of low doses were the benefits of this method, especially for fetal samples where there is a limited blood volume which limits of the volume of plasma that can be obtained for analysis.

The recovery was in an acceptable range for both rosiglitazone and IS. The liquid–liquid extraction method employed was simple, sensitive and provided clean chromatograms comparable to the method of Pedersen et al. [12] which used a solid–phase extraction method. Their method had a LLOQ of 1 ng/ml using 500 μl of plasma, which is slightly lower than our LLOQ of 2.5 ng/ml. Our method, however, used only 200 μl of plasma (i.e. 40% of the volume, equating to a similar LLOQ per ml of sample), a simple liquid–liquid extraction, shorter run time and less total consumption of organic solvents in comparison with their method. Although these authors had an upper limit of 1000 ng/ml for their standard curve, this is excessive for our requirements as the expected plasma concentration at steady state in our pharmacokinetic study was not higher than 30 ng/ml. Whether our method can be applied over the range employed by Pedersen et al. [12] is yet to be determined.

Another well documented method for detection of rosiglitazone in human plasma by HPLC was reported by Hruska et al. [10]. They used a simple precipitation method with a LLOQ of 5 ng/ml, however, the run time for sample analysis in their method was longer (retention time of rosiglitazone in our method was 9 min and for their method was 13 min) than in our study. Our method, with a LLOQ of 2.5 ng/ml and shorter run time offers some efficiency advantage.

There are published methods for detection of rosiglitazone using mass spectrometry [8,9], with the LLOQ range of 1–5 ng/ml which is comparable to our LLOQ of 2.5 ng/ml. The sample preparation of our method is similar in simplicity to these methods; however, access to mass spectrometry is a limitation in many research laboratories and has much greater cost implications in its use.

The pharmacokinetics of rosiglitazone in man are well established with a half-life ($t½$) of 4 h and clearance of 2.7 l/h. The reported $t½$ in rats (1.4 h) is similar [13]. For rosiglitazone, the main route of elimination in humans and other species is via hepatic clearance where it is metabolized mostly by CYP2C8 and CYP2C9 [14], but its metabolism in the sheep is yet to be investigated. Moreover, fetal hepatic xenobiotic metabolic capacity is not fully understood, particularly in the sheep. However, it is likely that hepatic metabolism of rosiglitazone in the sheep fetus is underdeveloped or absent altogether which, alongside the absence of rosiglitazone in the amniotic fluid, suggests that elimination of rosiglitazone from the fetus is limited to placental clearance consistent with limited evidence showing an absence of rosiglitazone in human amniotic fluid [4].

One of the key roles of the placenta is to prevent the passage of potentially toxic xenobiotics from the maternal to the fetal circulation. Nevertheless, drugs can cross the placenta and pose a risk to the developing fetus. In the absence of other clearance mechanisms, the placenta plays a significant role in fetal drug clearance, and indeed many drugs, including labetalol [15], metoclopramide [16] and diphenhydramine [17], are preferentially transported from the fetus to the maternal circulation. The model used in this study is unusual in that the drug is dosed directly to the fetus, rather than to the ewe, with the intention of allowing the drug to accumulate and hence exert a sustained effect on fetal PPAR-γ receptors. As our data show significant concentrations of rosiglitazone in fetal blood, this indicates that it is feasible to dose the fetus directly by rosiglitazone infusion and obtain good plasma concentrations. However, the fetal:maternal plasma rosiglitazone concentration ratio (F:M) is highly variable over the 15 days measured which may prove problematic when designing a suitable infusion rate.

We therefore need to determine the extent of placental clearance to allow us to determine the optimal infusion rate of rosiglitazone to maintain adequate fetal concentrations. In this pilot study, the F:M ratio was calculated to ascertain whether there is accumulation of rosiglitazone in the fetus (indicated by a F:M > 1), whether there is free distribution (F:M = 1) or active efflux of rosiglitazone by the placenta (F:M < 1). As illustrated in Fig. 4, F:M is constantly greater than 1 in our pilot data, which suggests that rosiglitazone accumulates in the fetus. This is in conflict with previous data in humans which demonstrate rosiglitazone is a substrate for p-glycoprotein suggesting that rosiglitazone concentrations in the fetus are lower than in the maternal circulation [4]. However, in this study the drug is dosed directly to the fetus, rather than the maternal circulation as in the previous work [4]. It is possible that, although the sheep does express p-glycoprotein with very high homology to humans [18], dosing directly to the fetus results in rosiglitazone concentrations sufficient to saturate p-glycoprotein-mediated efflux transport in the placenta which may contribute to the fetal accumulation. Nevertheless, the F:M ratio in our pilot data was obtained in a single sheep and requires further investigation for confirmation of this observation.

There are several possible explanations for the observed variability over time in fetal plasma concentrations and F:M plasma ratio. Under normal circumstances it is assumed that when an infusion is commenced the plasma concentration of the drug will accumulate until it reaches steady state at which time it will reach a plateau. However, this will only be true if the physiological parameters affecting the drug's pharmacokinetics remain constant. The rosiglitazone infusion in this study was conducted over a long period of time (15–17 days) and in this time there will be rapid fetal growth and physiological changes. It is possible that fetal liver maturity and placental changes affect the ability to transfer and metabolize drugs which, alongside an increasing uterine blood flow, might be expected to reduce fetal plasma concentrations. However, as the fetus develops the concentration of plasma albumin increases, which has the ability to bind rosiglitazone (normally 99.8% bound to plasma albumin). At the same time maternal plasma albumin would be expected to become more dilute due to plasma expansion associated with pregnancy, reducing its binding capacity. The logical net effect of this is accumulation of highly bound drugs such as rosiglitazone in the fetal plasma. This appears to be supported by the trend in the data in Fig. 4 from the pilot data in a single animal reported here. Accumulation of rosiglitazone over time may not be as problematic as it first appears provided that the free drug in the fetus (rather than free + bound) remains reasonably constant. However, further development of the model, and its application in a larger number of animals is required to determine whether this is the case.

5. Conclusion

The developed assay is simple, sensitive, and accurate for the determination of rosiglitazone in sheep plasma and amniotic fluid. The method utilizes small amounts of plasma and sample preparation is simple. The range of the calibration curve is ideal for pharmacokinetic studies in the sheep fetal model. The method was successfully applied to the determination of rosiglitazone in the pregnant ewe and her fetus.

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