AASV Foundation – FINAL Report

Title:

- Investigating the plasma pharmacokinetics and tissue residues of oral firocoxib following transmammary delivery from sows to piglets.

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Statement of problem:

In the US, no drugs are currently labeled by the Food and Drug Administration (FDA) to alleviate pain in swine. Therefore, the development of pain mitigation strategies that address consumer concerns about animal welfare while still being safe, effective, practical and economical to administer are urgently needed for the swine industry to address emerging animal welfare challenges. In a recent study evaluating a transmammary route of administration for firocoxib, we reported a significant reduction in plasma cortisol concentrations and an increase in average daily gain in bodyweight (ADG) from processing to weaning in piglets nursing sows that received 2 mg/kg IM of firocoxib. However, this required intramuscular injection volumes of 20 to 30 mL of firocoxib. This dose volume may be inconvenient for caregivers to administer in many commercial pork production systems. Furthermore, this could potentially create challenges in regards to compliance with Pork Quality Assurance (PQA) standards, specifically due to muscle damage and the potential for broken injection needles. Therefore, we proposed to investigate the pharmacokinetics of oral firocoxib in sows. The pharmacokinetic data can then be used to further optimize an oral dose of firocoxib intended for transmammary delivery to piglets.

Objective(s):

- Describe the pharmacokinetics (PK) and bioavailability of oral firocoxib in sows.
- Describe the tissue residue concentrations of firocoxib in sows following oral administration.

Brief materials and methods:

• Seven sows were enrolled onto the study. The study was conducted in two phases with a 23 day washout period between the IV dosing of 0.5 mg/kg in phase 1, and oral dosing of 4 mg/kg in phase 2. Whole blood was obtained at predetermined time points for plasma firocoxib determination. Time point for blood sampling following IV administration were 0, 5, 10, 20, 30, 60 minutes and 4, 8, 12, 24, 48 and 72 h; and 0, 2, 4, 6, 8, 12, 24, 48, 72, 96, and 120 h following oral administration. One sow was removed following oral administration due to becoming refractory to blood sampling. Sows were humanely euthanized and tissue samples collected for firocoxib concentrations at 5 (n=2), 10 (n=2), and 21 (n=3) days following oral firocoxib administration at 4 mg/kg. Plasma and tissue firocoxib concentrations were determined using a validated LC-MS method developed and published by our research group. The pharmacokinetics of firocoxib in sows following IV and oral dosing were determined via non-compartmental analysis using commercial computer software. Bioavailability was dose adjusted by multiplying the AUC after oral administration with the IV dose and dividing this by the AUC after IV administration multiplied by the oral dose.

Significant results:.

• Pharmacokinetic parameters are presented in Table 1.

• Tissue firocoxib concentrations are presented in Table 2.

• No macroscopic lesions were observed on post-mortem exam. Microscopic examination of liver and kidney sections were within normal limits. Mild gastritis was observed in three of seven sows. No evidence of NSAID intoxication was observed in tissue sections examined

Table 1. (a) Mean pharmacokinetic parameters of firocoxib following single oral (PO) administration at the dose rate of 4 mg/kg body weight in adult sows (n = 6). (b) Mean pharmacokinetic parameters of firocoxib following single intravenous (IV) administration at the dose rate of 0.5 mg/kg body weight in adult sows (n = 7).

Parameter	Unit	Geometric Mean	SD	Median	Range
(a)					
λ_z	1/h	0.03	0.02	0.03	0.02 – 0.06
$T^1/_2$	h	22.5	9.47	23.53	11.14 – 40.25
Tmax	h	7.41	8.00	9.00	2.00 – 24.00
Cmax	µg/mL	0.06	0.02	0.06	0.04 – 0.11
$AUC_{0-\infty}$	h x µg/mL	2.57	0.70	2.70	1.55 – 3.40
AUC extrapolated	%	2.32	5.08	3.59	0.10 – 14.56
$AUMC_{0-\infty}$	h^2 x µg/mL	98.31	62.25	109.89	37.45 – 216.39
$MRT_{0-\infty}$	h	38.18	13.89	39.11	24.20 – 63.64
MAT	h	21.61	10.97	24.33	9.88 – 40.09
F	%	70.30	25.76	67.17	52.72 – 119.50
(b)					
C_0	µg/mL	18.57	4.47	17.71	14.07 – 26.58
λ_z	1/h	0.04	0.01	0.04	0.03 – 0.06
$T^1/_2$	h	16.61	3.49	16.93	12.38 – 21.89
AUC_{0-24h}	h x µg/mL	0.34	0.11	0.37	0.22 – 0.52
AUC_{0-last}	h x µg/mL	0.43	0.17	0.49	0.25 – 0.74
$AUC_{0-\infty}$	h x µg/mL	0.44	0.19	0.51	0.25 – 0.81
AUC extrapolated	%	2.94	2.19	3.62	1.41 – 7.79
$AUMC_{0-\infty}$	h^2 x µg/mL	6.64	5.58	8.10	2.52 – 18.99
$MRT_{0-\infty}$	h	14.92	4.71	14.48	10.03 – 23.55
Vss	L/kg	16.75	3.20	16.05	12.95 – 22.08
Vz	L/kg	26.92	6.24	28.55	18.81 – 35.52
Cl	L/h/kg	1.12	0.48	0.98	0.62 – 1.98

Table 2. Residue levels of firocoxib (µg/g) in collected tissues from sows 5, 10, and 21 days after administration of firocoxib at 4 mg/kg orally (PO).

Days post-dose	Animal ID	Liver (µg/g)	Kidney (µg/g)	Muscle (µg/g)	Skin & Fat (µg/g)
5	60241	1.59	0.35	0.13	1.45
	3816	0.52	0.12	0.03	0.05
10	853	<0.01	<0.01	NF	<0.01
	2743	0.03	<0.01	<0.01	0.03
21	243	<0.01	NF	NF	NF
	1451	<0.01	NF	NF	NF
	1458	<0.01	<0.01	<0.01	0.02

Discussion of how results can be applied by practitioners:

The observed apparent half-life (T½) values for firocoxib administered by both the IV and PO routes are longer than those published for meloxicam (IV; 6.2 h and PO; 6.8 h) and flunixin (IV; 6.3 h and PO; 7.1 h) when given to sows by the same routes of administration (Pairis-Garcia, Karriker et al., 2013; Pairis-Garcia, Johnson et al., 2015). The time to maximum concentration (Tmax; 7.4 h) was longer than reported for sows administered flunixin (1.0 h) and meloxicam (2.4 h). Additional work is needed to further characterize the Tmax, and if the role of fasting plays a role in absorption from the GI tract. Firocoxib in swine has a large volume of distribution (Vss) when compared to the Vss reported for other NSAIDS in swine. The Vss determined following IV administration in this study was 16.75 L/kg. This compares to 0.16 L/kg reported for sows administered IV meloxicam (Pairis-Garcia, Johnson et al., 2015) and 0.3 L/kg for sows administered IV flunixin (Pairis-Garcia, Karriker et al., 2013). The dose adjusted bioavailability of firocoxib was 0.7. This is similar to meloxicam at 0.8 and both are greater than oral flunixin bioavailability of 0.2.

Oral dosing of firocoxib at 4 mg/kg may be a viable alternative to IM injections if firocoxib is being used in nursing sows for transmammary analgesia. Given the large volume of distribution and long apparent half-life; firocoxib appears to be well suited as an analgesic to sows and transmammary analgesia to nursing piglets. Since firocoxib was identified in the tissues of one sow at 21 days post-administration, further work in establishing a meat with hold interval is needed.

Table 3. Comparison of firocoxib to meloxicam and flunixin when given by intravenous (IV) injection or oral (PO) administration.

	Firocoxib		Meloxicam		Flunixin	
Parameter, unit	IV	PO	IV	PO	IV	PO
Dose, mg/kg	0.5	4.0	0.5	0.5	2.2	2.2
Half-life, h	16.6	22.5	6.2	6.8	6.3	7.1
Time to peak concentration, h	-	7.4	-	2.4	-	1.0
Peak concentration, µg/mL	-	0.06	-	1.1	-	0.95
$AUC_{0-\infty}$, h x µg/mL	0.44	2.57	13.2	11.6	21.6	4.8
Volume of Distribution, L/kg	16.75		0.16		0.3	
Bioavailability	-	0.70	-	0.87	-	0.22

References

Pairis-Garcia, M.D., Johnson, A.K., KuKanich, B., Wulf, L., Millman, S.T., Stalder, K.J., Karriker, L.A. & Coetzee, J.F. (2015) Pharmacokinetics of meloxicam in mature swine after intravenous and oral administration. *J Vet Pharmacol Ther*, **38**(3), 265-270. https://doi.org/10.1111/jvp.12170

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