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Studies on the Pharmacokinetics of Melamine in Dairy Goat

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Abstract: This experiment was conducted to study the pharmacokinetics of melamine in dairy goat. A single intravenous administration of the melamine at the dose of 6.13 mg kg^{-1} B.W. to 6 dairy goats. Blood samples were collected at different intervals after administration and concentrations of melamine were determined by HPLC Method. The plasma concentration-time data of melamine was analyzed by Pharmaceutical 3P97. The results showed that two-compartment open model was the optimum one of melamine in the dairy goats. The main pharmacokinetic parameters were as follows: V_d was (0.03±0.01) L kg^{-1}, $t_{1/2\beta}$ was (3.64±0.02) h, AUC was (41.96±0.52) μg h mL^{-1}, Cl was (0.14±0.01) L kg^{-1} h^{-1}. These results indicated that the distribution of melamine in dairy goat was limit and the elimination of melamine was rapid.

Key words: Melamine, pharmacokinetics, dairy goat, HPLC, goat

INTRODUCTION

Melamine ($C_3N_6H_6$) is a stable carbon and nitrogen based compound which is processed with formaldehyde into resins used in the production of wood-based panels, laminates for kitchen cabinets, floors, table tops, coating for the automobile industry. But because of its high nitrogen content, it has been discovered that melamine has been deliberately added to raw milk or feed in order to boost its apparent protein content.

In 2007, there was a large outbreak of renal failure in cats and dogs in the USA associated with ingestion of pet food found to contain melamine and cyanuric acid. An increased incidence of kidney stones and renal failure in infants has been reported in 2008, believed to be associated with the ingestion of infant formula contaminated with melamine (Burns, 2007). Previous pharmacokinetics studies of melamine in male Fischer rats and pigs has been reported (Buur *et al*., 2008; Baynes *et al*., 2008) but the pharmacokinetics studies of melamine in ruminants has not been shown.

The purpose of this study was to characterize the disposition of melamine in dairy goat as its pharmacokinetics in this species has not been described in the literature. Data from this intravenous study can be used to accurately assess such kinetic parameters as half-life, volume of distribution and clearance of this contaminant in dairy goat which is required for accurately predicting plasma concentration and the time of milk discarding in dairy goats exposed to similar or larger doses.

MATERIALS AND METHODS

Animal: Six healthy Guan Zhong dairy goats of 35 (±2.65) kg were acclimated for 1 week prior to surgery, animals were held off feed and water the night before surgery.

Intravenous catheter surgical implantation: On the day of surgery, anesthesia was induced with an intramuscular injection of Lumianbao. The left jugular was identified by surgical cut-down using an aseptic technique. A gauge polyethylene catheter was advanced through jugular vein approximately 5 cm. The incision was closed and the catheter was secured around the neck of the animal. The penicillium and streptomycin were injected through the muscle twice everyday until the 7 days of the surgery.

Animal dose and sampling: A single intravenous administration of the melamine at the dose of 6.13 mg kg^{-1} B.W. to 6 dairy goats. The week following surgery, a

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3-5 mL blood sample was drawn at 0, 0.08, 0.25, 0.50, 0.75, 1, 2, 4, 8, 12 and 24 h post dose from the jugular catheter and replaced with lactated ringers solution. Blood was drawn into heparinized tubes, spun immediately and plasma was decanted. The plasma was frozen at -20°C until processed. All samples were analyzed within 1 week of the study.

Sample extraction: Plasma samples were thawed, sample was extracted through trichloroacetic acid-zinic acetate solution which was purified with solid phase extraction cartridge (MCX, Dikma). The extraction was isolated by on a Dikma C18 column. The buffer was the mixed solution of citric acid and sodium octane sulfonate and the mobile phase were buffer-acetonitrile. The flow rate was 1.0 mL min^{-1}. Column temperature was 25°C. UV-detection was performed at 240 nm. The concentrations of melamine were determined by HPLC Method and the plasma concentration-time data of melamine was analyzed by Pharmaceutical 3P97.

RESULTS AND DISCUSSION

The results showed that two-compartment open model was the optimum one of melamine in the dairy goats. Table 1 showed the plasma concentration of melamine (6.13 mg kg^{-1} after intravenous in dairy goat. Table 2 showed the pharmacokinetic parameters after intravenous in dairy goat. The main pharmacokinetic parameters were as follows: V_d was (0.03±0.01) L kg^{-1}, $t_{1/2\beta}$ was (3.64±0.02) h, AUC was (41.96±0.52) μg h mL^{-1}, Cl was (0.14±0.01) L kg^{-1} h^{-1}.

This is the first study to report on the Intravenous (IV) pharmacokinetics of melamine in ruminant species. The previously reported pharmacokinetic study described the plasma and tissue kinetics of melamine in Fischer 344 rats following oral gavage without companion IV data (Mast *et al*., 1983). The study by the nature of its design provides an accurate assessment of the disposition of melamine in dairy goats that is its distribution and elimination without the many confounding factors associated with oral absorption or other extravascular routes of administration.

The same dose of melamine and administration mode with the pig was selected to compare the difference of the melamine pharmacokinetics (Baynes *et al*., 2008). The results showed that two-compartment open model was the optimum one of melamine in the dairy goats. Melamine appears to be cleared rapidly ($T_{1/2}$ = 3.64±0.02 h) in the dairy goat. The half-life of melamine in the pig ($T_{1/2}$ = 4.07±0.39 h) appears to be 1.1 times longer than that in the dairy goat and this is primarily due to an almost 1.4 fold greater renal clearance in the dairy goat than the pig which demonstrated that tissue distribution may be the most important parameter to estimate the time of elimination.

Table 1: Plasma concentration of melamine (6.13 mg kg^{-1}) after intravenous in dairy goat (n = 6)

	Concentration of melamine/(μg mL^{-1})						
Time (h)	1	2	3	4	5	6	X±SD
0	ND	ND	ND	ND	ND	ND	ND
0.08	70.28	65.24	69.31	68.34	63.80	69.28	67.71±1.06
0.25	8.85	9.35	11.69	9.87	10.27	11.49	10.25±0.47
0.50	5.90	5.28	5.76	5.67	5.50	6.08	5.70±0.12
0.75	5.07	4.97	5.16	5.11	4.95	5.20	5.08±0.04
1	4.46	4.35	4.99	5.02	4.62	4.71	4.69±0.11
2	3.39	3.29	3.41	3.01	3.28	4.03	3.40±0.14
4	1.98	2.02	2.15	2.11	1.98	2.03	2.05±0.03
8	1.85	1.99	2.05	1.54	1.66	2.16	1.88±0.10
12	0.52	0.58	0.51	0.52	0.53	0.54	0.53±0.01
24	ND	ND	ND	ND	ND	ND	ND

ND = Not Discover

Table 2: Pharmacokinetic parameters after intravenous in dairy goat (n = 6)

Parameters (units)	X±SD
A (μg mL^{-1})	203.31±12.20
α (h^{-1})	14.45±1.620
B (μg mL^{-1})	5.23±0.160
β (h^{-1})	0.15±0.010
V_d (L kg^{-1})	0.03±0.010
$t_{1/2\alpha}$ (h)	0.05±0.010
$t_{1/2\beta}$ (h)	3.64±0.020
AUC (μg h mL^{-1})	41.96±0.520
CL(s) (L kg^{-1} h^{-1})	0.14±0.010

A = Parameters of distribution; α = Distributed speed of two-compartment; B = Parameters of elimination; β = Eliminated speed of two-compartment; V_d = Volume of distribution; $t_{1/2\alpha}$ = Half-life of distribution; $t_{1/2\beta}$ = Half-life of elimination; AUC = Area Under the Curve extrapolated to infinity; Cl = Clearance

This is in spite of the fact that the apparent volume of distribution in the dairy goat study (0.03 L kg^{-1}) appears to be greatly lower than that the 1 L kg^{-1}. The limited distribution in the dairy goats is consistent with data from the earlier rat study which demonstrated that tissue distribution may be limited to the total body water and possibly binding to the kidney which is the organ primarily responsible for its clearance.

CONCLUSION

This study demonstrated that melamine is rapidly eliminated by the kidney and probably not widely distributed to various tissues in the dairy goats and there should be no concerns about extensive binding to tissues that may be consumed by the public should a dairy goat be exposed to melamine. Dairy goat's blood would be cleared of about 99% of the melamine dose within seven half-lives or 25.4 h after exposure and this blood concentration should be below the safe level. These rat studies also demonstrated that the half-life of melamine in the kidney may be 7 fold greater than in the plasma which

makes estimation of a safe withholding time very difficult to predict based on melamine depletion in the kidney (USDA, 2007). But researchers can accurately predict plasma concentration and the time of milk discarding in dairy goats exposed to similar or larger doses. These results indicated that the distribution of melamine in dairy goat was limit and the elimination of melamine was rapid. Further studies are required to determine the depletion kinetics of melamine in dairy goats to provide a better estimate of when melamine levels in the kidney will be below the safe levels (Baynes *et al*., 2008).

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