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Metabolism of Metamitron in Goat Following a Single Oral Administration of a Nontoxic Dose Level: A Continued Study

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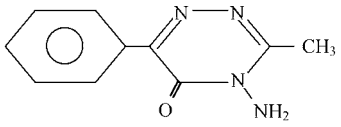
Disposition kinetic behavior and metabolism studies of metamitron and its metabolite in terms of the parent compound were carried out in black Bengal goats after a single oral administration of a nontoxic oral dose at 30 mg kg^{-1} of body weight. Metamitron was detected in the blood sample at 5 min (2.23 ± 0.04 μg mL^{-1}), maximum at 1 h (3.43 ± 0.02 μg mL^{-1}) and minimum at 12 h (0.41 ± 0.01 μg mL^{-1}), after a single oral administration. Metabolite [3-methyl-6-phenyl-1,2,4-triazin-5(4*H*)-one] in terms of the parent compound was detected in the blood sample at 5 min (0.47 ± 0.006 μg mL^{-1}), maximum at 6 h (5.12 ± 0.02 μg mL^{-1}) and minimum at 96 h (1.06 ± 0.016 μg mL^{-1}), after a single oral administration. The $t_{1/2K}$ and Cl_B values of metamitron were 3.63 ± 0.05 h and 1.36 ± 0.016 L kg^{-1} h^{-1}, respectively, whereas the $t_{1/2K}{}^m$ and $Cl_B{}^m$ values of the metabolite were 38.15 ± 0.37 h and 0.091 ± 0.001 L kg^{-1} h^{-1}, respectively, which suggested long persistence of the metabolite in blood and tissues of goat. Metamitron was excreted through feces and urine for up to 48 and 72 h, whereas the metabolite was excreted for up to 168 and 144 h, respectively. Metabolite alone contributed to 96 and 67% of combined recovery percentage of metamitron and metabolite against the administered dose in feces and urine of goat, respectively. All of the goat tissues except lung, adrenal gland, ovary, testis, and mammary gland retained the metabolite residue for up to 6 days after administration.

KEYWORDS: Kinetics; nontoxic dose; recovery; metamitron; metabolite; goat

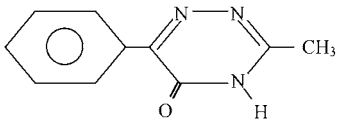
INTRODUCTION

The herbicidal property of metamitron was first reported in 1975 by Schmidt et al. (*1*). The photodecomposition of metamitron in soil has been demonstrated, and in water, photolysis produced deamination to deaminometamitron (*2*). The chemical structures of metamitron and its metabolite are shown in **Figure 1**. We have reported toxicokinetic behavior, recovery, and metabolism of metamitron in goat following oral administration at a toxic dose level (*3*). The present work is carried out after oral administration of a nontoxic oral dose of metamitron. The objective is to find the difference in kinetic behavior between toxic and nontoxic dose levels. Besides, the kinetic behavior of the metabolite [3-methyl-6-phenyl-1,2,4-triazin-5(4*H*)-one] in terms of the parent compound and recovery can be evaluated on a comparative basis. The work is carried out in small ruminant black Bengal goats. The data generated thereof will reveal the kinetic behaviors of the parent compound as well as its metabolite in terms of the parent compound and metabolism in goats at the maximum nontoxic dose level.



[4−amino-3-methyl-6-phenyl-1,2,4−triazin-5(4H)-one]

Metamitron



[3-methyl-6-phenyl-1,2,4−triazin-5(4H)-one]

Metabolite

Figure 1. Structures of metamitron and metabolite.

EXPERIMENTAL PROCEDURES

Chemicals. Metamitron (technical grade, purity = 98%) and its metabolite, 3-methyl-6-phenyl-1,2,4-triazin-5(4*H*)-one (purity = 98%),

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were supplied by M/S Gharda Chemicals Ltd., Mumbai, India. These compounds were further purified and authenticated by TLC followed by HPLC and spectroscopic (UV, IR, MS, and NMR) analyses. All of the solvents and chemicals used in this study were of analytical grade and purchased from E. Merck and Sigma Chemical Co..

Animal Treatment. Healthy adult black Bengal male and female (nulliparous) goats of 1.5−2 years of age, weighing between 9.5 and 12 kg, were selected. The goats were acclimatized individually in stainless steel metabolic cages and provided with artificial fluorescent lighting, controlled temperature (22 ± 3 °C), water, and standard feed (*4*). Each animal was fasted overnight before treatment.

Determination of Maximum Nontoxic Oral Dose. Metamitron at 30 mg kg^{-1} has been fixed as the maximum nontoxic oral dose in our previous study (*3*).

Kinetics. Blood samples were collected from the jugular vein of each experimental goat into heparinated tubes at different time intervals (0.08, 0.25, 0.5, 1, 2, 4, 6, 8, 12, 24, 48, 72, and 96 h) after metamitron administration in duplicate sets of test tubes separately. The concentrations of metamitron and its metabolite [3-methyl-6-phenyl-1,2,4-triazin-5(4*H*)-one] were estimated by HPLC.

The values of kinetic parameters such as K_a, $t_{1/2K_a}$, K, $t_{1/2K}$, T/B, AUC, K_{el}, Cl_B, K_{12}, K_{21}, F_c, K^m, $t_{1/2K}{}^m$, $Cl_B{}^m$, V^m, $C^m{}_{max}$, and $T^m{}_{max}$ were determined from semilogarithmic plots of mean blood concentration time profile data in goats using standard formulas (*5*−*7*).

Collection of Samples. Urine and feces were collected from individual goats at 24, 48, 72, 96, 120, 144, and 168 h after oral administration. Each collection period represented the total urine and feces production for the preceding 24 h period. The excretion was measured or weighed and stored at −20 °C prior to extraction.

The animals of the first, second, third, and fourth groups were sacrificed on days 4, 5, 6, and 7 after dosing, respectively. Samples of liver, kidney, lung, brain, heart, spleen, adrenal gland, omental fat, ovary, uterus, testis, rumen, mammary gland, reticulum, omasum, abomasum, intestine, bile, contents of rumen and intestine, thigh muscle, bone, and skin were taken, weighed, minced, packed, and stored at −20 °C prior to extraction. A sample (2 g) of each of the above-mentioned tissues except bile (2 mL) and urine (10 mL) was extracted with respective solvent, and metamitron and its metabolite were quantified and thereafter multiplied with respective factors to get the total recovery. Because it is difficult to collect and weigh the whole muscle, skin, and bone, a representative sample (2 g for muscle and skin and 30 g for bone) of each was extracted with respective solvent, quantified, and multiplied with a factor as described by Davis et al. (*8*) to get the total recovery.

Extraction and cleanup of metamitron and its metabolite from blood, bile, urine, feces, and tissues were made following the method described earlier (*3*).

Quantification. A Hewlett-Packard (model 1050) liquid chromatograph coupled with a variable-wavelength UV−vis detector attached to a 3392A integrator was used for the analysis of metamitron and its metabolite with the following operational parameters: column, Spherisorb, 125 × 4 mm, ODS2 5 μm, made of stainless steel; mobile phase, acetonitrile /water (1:1). The mixture was subjected to membrane filtration and degassed by ultrasonification: λ value, 306 nm; flow rate, 0.3 mL min^{-1}; injection using a 25 μL loop with a Hamilton syringe. Standard and samples (20 μL) were injected into the liquid chromatograph with the first and last being the standard.

Chromatographic Procedure. Stock solutions of metamitron and its metabolite [3-methyl-6-phenyl-1,2,4-triazin-5(4*H*)-one] (100 ppm) were prepared in acetonitrile as standards. The retention times of metamitron and metabolite were 4.8 and 3.36 min, respectively. The retention times of parent and metabolite occurring in blood/feces/urine/tissue were compared with that of the external standard, and the data were recorded in an HP3392A integrator.

Procedure of Recovery. The recoveries of metamitron and its metabolite were estimated following fortification of different substrates with known quantities to give final concentrations of 0.5, 1.0, 2.0, and 4.0 ppm for blood, urine, and bile and 1.0, 2.0, 4.0, and 8.0 ppm for feces, tissues, and gastrointestinal contents. The recoveries of metamitron and its metabolite from blood, urine, and other substrates ranged from 86 to 96%. The limit of detection for metamitron and its metabolite was found to be 0.1 ppm. The limit of quantification was 0.15 ppm.

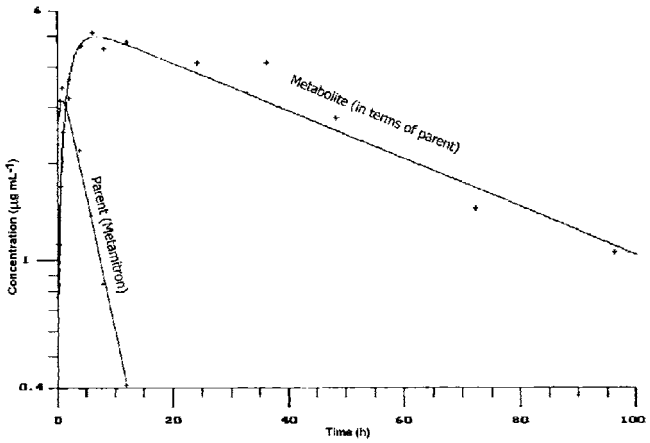

Figure 2. Semilogarithmic plot of mean blood concentration (μg mL^{-1}) of metamitron and its metabolite (in terms of parent compound) against time with computerized best-fit line following oral administration of a single nontoxic dose of metamitron at 30 mg kg^{-1} in goats.

Table 1. Kinetic Parameters of Metamitron[a] after a Single Oral Administration to Goats at 30 mg kg^{-1} ($n = 6$; Mean ± SE[b] Values for both Males and Females)

parameter	value	parameter	value
K_a (h^{-1})	2.02 ± 0.12	F_c	0.68 ± 0.004
$t_{1/2K_a}$ (h)	0.349 ± 0.02	K_{el} (h^{-1})	0.27 ± 0.004
K (h^{-1})	0.19 ± 0.002	K_{12} (h^{-1})	0.55 ± 0.04
$t_{1/2K}$ (h)	3.63 ± 0.05	K_{21} (h^{-1})	1.39 ± 0.08
$V_{d,area}$ (L kg^{-1})	7.11 ± 0.04	T/B	0.45 ± 0.009
AUC (μg h mL^{-1})	17.47 ± 0.31	Cl_B (L kg^{-1} h^{-1})	1.36 ± 0.016

[a] Test chemical. [b] SE, standard error; K_a, absorption rate constant; $t_{1/2K_a}$, absorption half-life; K, elimination rate constant; $t_{1/2K}$, elimination half-life; $V_{d,area}$, apparent volume of distribution; AUC, total area under the blood herbicide concentration versus time curve; F_c, fraction of herbicide in central compartment; K_{el}, first-order rate constant of herbicide elimination from the central compartment; K_{12}, rate constant for transfer of herbicide from the central to peripheral compartment; K_{21}, rate constant for transfer of herbicide from the peripheral to central compartment; T/B, tissue/blood ratio; Cl_B, total body clearance.

metabolite in terms of parent compound:

$$\frac{\text{molecular weight of metabolite}}{\text{molecular weight of parent}} = \text{effective ratio (ER)}$$

$$\text{quantity of metabolite recovered} \div \text{ER} = \text{parent compound}$$

RESULTS

Metamitron and Metabolite in Blood. The initial concentration of metamitron in blood at 5 min was found to be 2.23 ± 0.04 μg mL^{-1}. Maximum concentration was recorded at 1 h (3.43 ± 0.02 μg mL^{-1}), and then the concentration declined (**Figure 2**) until 12 h (0.41 ± 0.01 μg mL^{-1}). Metamitron could not be detected in the blood sample of goat at 24 h.

The metabolite [3-methyl-6-phenyl-1,2,4-triazin-5(4*H*)-one] was detected in blood at 5 min (0.47 ± 0.006 μg mL^{-1} in terms of the parent compound); maximum concentration was recorded at 6 h (5.12 ± 0.02 μg mL^{-1} in terms of the parent compound), and thereafter the concentration very slowly declined (**Figure 2**) until 96 h (1.06 ± 0.01 μg mL^{-1} in terms of the parent compound).

The K_a, $t_{1/2K_a}$, K, $t_{1/2K}$, K_{el}, K_{12}, K_{21}, $V_{d,area}$, AUC, F_c, Cl_B, and T/B values of metamitron are presented in **Table 1**. Likewise, the K_m, $t_{1/2K}{}^m$, $Cl_B{}^m$, V^m, $C^m{}_{max}$, and $T^m{}_{max}$ values of

Table 2. Kinetic Parameters of the Metabolite [3-Methyl-6-phenyl-1,2,4-triazin-5(4*H*)-one] in Terms of the Parent Compound after a Single Oral Administration of Metamitron[a] at 30 mg kg^{-1} to Goats ($n = 6$; Mean ± SE[b] Values for both Males and Females)

parameter	value	parameter	value
K^m (h^{-1})	0.50 ± 0.007	V^m (L)	5.02 ± 0.05
$t_{1/2K}{}^m$ (h)	38.15 ± 0.37	$C^m{}_{max}$ ($\mu g\ mL^{-1}$)	5.26 ± 0.04
$Cl_B{}^m$ ($L\ kg^{-1}\ h^{-1}$)	0.09 ± 0.001	$T^m{}_{max}$ (h)	6.76 ± 0.06

[a] Test chemical. [b] SE, standard error; K^m, metabolism rate constant; $t_{1/2K}{}^m$, biological half-life of metabolite in terms of parent compound; $Cl_B{}^m$, total body clearance of metabolite in terms of parent compound; V^m, apparent volume of distribution of metabolite in terms of parent compound; $C^m{}_{max}$, maximum blood concentration of metabolite in terms of parent compound; $T^m{}_{max}$, time at maximum metabolite concentration in terms of parent compound in blood.

the metabolite [3-methyl-6-phenyl-1,2,4-triazin-5(4*H*)-one] in terms of the parent compound are presented in **Table 2**.

Recovery of Metamitron and Its Metabolite. *Feces.* The excretion of maximum quantities of metamitron and metabolite was recorded at 24 h. Metamitron was not detected in the feces samples of goats collected at 72 h, whereas the metabolite of metamitron was detected in the feces samples of goats collected at 168 h of administration (**Table 3**).

Urine. The excretion of the maximum quantity of metamitron was recorded at 24 h, was complete by 72 h, and was below the detection limit in the 96 h sample. The metabolite was excreted through urine by 24 h, reached a maximum in the 48 h urine sample, and by 168 h had reached a level below the detection limit (**Table 4**).

Tissue. The mean residual concentrations of metamitron and its metabolite recovered from different tissues of goats are presented in **Table 5**. Liver, kidney, rumen, reticulum, abomasum, fat, small intestine, skin, bone, and large intestine retained the metamitron residue from the goats sacrificed on day 4, of which fat retained the maximum followed by rumen, small intestine, reticulum, and skin in sequence, whereas liver, reticulum, fat, small intestine, bone, large intestine, and rumen tissues retained the metamitron residue in goats sacrificed on day 5. Only bone retained the residue, whereas none of the tissues retained the metamitron residue in goats sacrificed on day 6, respectively. Except ovary, testis, and adrenal gland, all of the tissues retained the residue of the metabolite of metamitron in goats sacrificed on days 4 and 5, respectively.

Table 3. Metamitron and Its Metabolite Recovered from Feces (Parts per Million) on Wet Basis of Goats after Administration of a Single Oral Dose at 30 mg kg^{-1}[a]

	group of goats sacrificed on day							
	4		5		6		7	
time (h)	P	M	P	M	P	M	P	M
0–24	5.34 ± 1.10 (2.29)	61.67 ± 6.71 (26.52)	5.85 ± 1.28 (2.99)	69.13 ± 6.98 (35.26)	6.30 ± 0.96 (2.08)	52.84 ± 5.74 (16.64)	4.96 ± 1.39 (1.58)	53.70 ± 4.36 (16.39)
24–48	4.26 ± 1.08 (1.92)	38.80 ± 4.49 (17.46)	3.92 ± 1.02 (2.08)	49.80 ± 6.05 (26.39)	2.97 ± 0.07 (1.01)	46.60 ± 5.39 (14.90)	4.53 ± 0.48 (1.40)	45.58 ± 3.63 (14.12)
48–72	BDL	32.75 ± 4.71 (13.74)	BDL	34.05 ± 6.43 (17.02)	BDL	44.65 ± 6.61 (14.73)	BDL	46.39 ± 4.35 (13.90)
72–96	BDL	20.80 ± 1.57 (10.19)	BDL	21.93 ± 2.73 (12.72)	BDL	36.55 ± 5.25 (13.51)	BDL	39.64 ± 4.36 (13.86)
96–120	–	–	BDL	13.54 ± 3.15 (8.26)	BDL	33.99 ± 4.63 (12.84)	BDL	34.57 ± 3.92 (12.78)
120–144	–	–	–	–	BDL	24.89 ± 1.59 (8.45)	BDL	29.49 ± 3.96 (9.42)
144–168	–	–	–	–	–	–	BDL	22.91 ± 2.32 (8.24)

[a] Mean value of six replicates with SE values of male and females; numbers in parentheses indicate mean total recovery in milligrams/day; BDL, below detection limit (<0.1 ppm); P, parent; M, metabolite; –, not applicable.

Table 4. Metamitron and Its Metabolite Recovered from Urine (Parts per Million) of Goats after Administration of a Single Oral Dose at 30 mg kg^{-1}[a]

	group of goats sacrificed on day							
	4		5		6		7	
time (h)	P	M	P	M	P	M	P	M
0–24	62.25 ± 3.50 (28.19)	43.56 ± 2.66 (19.72)	47.65 ± 7.84 (25.74)	36.77 ± 6.77 (19.87)	59.64 ± 7.57 (20.88)	23.91 ± 3.01 (17.22)	66.07 ± 8.38 (21.80)	27.45 ± 3.02 (9.02)
24–48	49.48 ± 8.79 (19.46)	89.28 ± 9.45 (35.10)	33.22 ± 7.01 (15.95)	72.60 ± 11.02 (34.85)	47.21 ± 5.73 (14.14)	89.72 ± 9.62 (26.08)	30.21 ± 2.56 (8.75)	84.20 ± 5.91 (24.42)
48–72	16.77 ± 3.80 (6.44)	73.85 ± 6.69 (28.31)	11.17 ± 2.56 (5.15)	61.25 ± 10.99 (28.19)	18.67 ± 2.50 (5.41)	57.50 ± 7.34 (11.08)	16.07 ± 2.45 (4.49)	81.85 ± 8.24 (22.99)
72–96	BDL	18.99 ± 4.57 (7.08)	BDL	17.23 ± 3.88 (7.75)	BDL	39.58 ± 3.62 (8.33)	BDL	40.55 ± 4.54 (10.95)
96–120	–	–	BDL	11.41 ± 2.30 (5.69)	BDL	16.76 ± 1.82 (5.35)	BDL	25.77 ± 3.02 (7.73)
120–144	–	–	–	–	BDL	8.51 ± 1.58 (2.37)	BDL	23.42 ± 3.78 (6.32)
144–168	–	–	–	–	–	–	BDL	BDL

[a] Mean value of six replicates with SE values of male and female; numbers in parentheses indicate mean total recovery in mlligrams/day; BDL, below detection limit (<0.1 ppm); P, parent; M, metabolite; –, not applicable.

Table 5. Metamitron and Its Metabolite Recovered (Parts per Million) from Different Tissues and Gastrointestinal Contents on Wet Basis of Goats Following Administration of a Single Oral Dose at 30 mg kg^{-1}[a]

	group of goats sacrificed on day							
	4		5		6		7	
substrate	P	M	P	M	P	M	P	M
liver	0.23 ± 0.01	1.71 ± 0.31	0.17 ± 0.03	1.54 ± 0.26	BDL	1.41 ± 0.21	BDL	1.09 ± 0.13
lung	BDL	0.70 ± 0.16	BDL	0.66 ± 0.14	BDL	BDL	BDL	BDL
spleen	BDL	2.26 ± 0.70	BDL	2.24 ± 0.69	BDL	1.57 ± 0.28	BDL	BDL
kidney	0.47 ± 0.08	2.57 ± 0.49	BDL	2.05 ± 0.68	BDL	1.35 ± 0.32	BDL	BDL
bile	BDL	3.21 ± 0.61	BDL	2.92 ± 0.51	BDL	2.57 ± 0.54	BDL	1.42 ± 0.39
heart	BDL	4.37 ± 0.78	BDL	4.02 ± 1.07	BDL	1.40 ± 0.44	BDL	BDL
adrenal gland	BDL	BDL	BDL	BDL	BDL	BDL	BDL	BDL
fat	2.95 ± 0.48	5.15 ± 1.06	2.56 ± 0.50	4.80 ± 0.99	BDL	0.59 ± 0.18	BDL	0.31 ± 0.08
rumen	1.27 ± 0.26	2.35 ± 0.68	1.13 ± 0.22	1.75 ± 0.32	BDL	0.95 ± 0.21	BDL	BDL
reticulum	0.83 ± 0.26	3.12 ± 0.53	0.69 ± 0.14	2.41 ± 0.44	BDL	2.18 ± 0.59	BDL	BDL
omasum	BDL	0.83 ± 0.16	BDL	0.67 ± 0.13	BDL	0.39 ± 0.08	BDL	BDL
abomasum	0.16 ± 0.009	1.15 ± 0.28	BDL	1.10 ± 0.29	BDL	0.78 ± 0.20	BDL	BDL
small intestine	0.92 ± 0.12	4.93 ± 0.55	0.62 ± 0.13	4.81 ± 0.61	BDL	4.55 ± 0.92	BDL	3.97 ± 0.74
large intestine	0.24 ± 0.09	0.89 ± 0.09	0.19 ± 0.02	0.80 ± 0.18	BDL	0.68 ± 0.12	BDL	0.49 ± 0.15
brain	BDL	1.93 ± 0.40	BDL	1.41 ± 0.28	BDL	0.95 ± 0.17	BDL	BDL
ovary	BDL	BDL	BDL	BDL	BDL	BDL	BDL	BDL
testis	BDL	BDL	BDL	BDL	BDL	BDL	BDL	BDL
uterus	BDL	1.01 ± 0.14	BDL	0.95 ± 0.17	BDL	0.74 ± 0.06	BDL	BDL
mammary gland	BDL	1.90 ± 0.47	BDL	1.13 ± 0.13	BDL	BDL	BDL	BDL
muscle	BDL	0.57 ± 0.04	BDL	0.46 ± 0.03	BDL	0.26 ± 0.04	BDL	BDL
skin	0.63 ± 0.006	1.22 ± 0.21	BDL	1.20 ± 0.17	BDL	0.96 ± 0.19	BDL	0.87 ± 0.15
bone	0.19 ± 0.04	1.69 ± 0.32	0.15 ± 0.01	1.56 ± 0.41	0.140.02	1.31 ± 0.26	BDL	1.20 ± 0.18
blood	BDL	1.80 ± 0.24	BDL	0.81 ± 0.14	BDL	0.78 ± 0.16	BDL	BDL
rumen content	BDL	2.77 ± 0.52	BDL	1.84 ± 0.43	BDL	1.36 ± 0.2	BDL	1.23 ± 0.39
large intestine contents	1.96 ± 0.79	18.33 ± 2.74	1.40 ± 0.32	17.65 ± 2.83	BDL	10.40 ± 1.85	BDL	9.98 ± 2.89
small intestine contents	5.06 ± 1.13	53.37 ± 7.44	4.33 ± 1.42	53.48 ± 4.66	BDL	43.21 ± 7.07	BDL	39.21 ± 6.20

[a] Mean value of six replicates with SE values of male and female; BDL, below detection limit (<0.1 ppm); P, parent; M, metabolite.

Table 6. Total Recovery Percentage of Metamitron and Its Metabolite from Goats Sacrificed on Different Days Following Administration of a Single Oral Dose at 30 mg kg^{-1}[a]

	group of goats sacrificed on day							
	4		5		6		7	
substrate	P	M	P	M	P	M	P	M
feces	1.16 (4.21)	20.39 (73.40)	1.3 (5.07)	27.62 (107.72)	1.03 (3.09)	28.25 (87.75)	0.99 (2.98	32.01 (96.03)
urine	15.02 (54.09)	27.08 (97.52)	12.01 (46.84)	26.70 (104.16)	13.47 (40.43)	25.50 (76.17)	11.68 (35.04	29.35 (88.06)
gastrointestinal content	0.98 (3.53)	14.63 (52.68)	0.79 (3.11)	10.50 (40.96)	BDL	9.65 (28.97)	BDL	8.64 (25.92)
tissue	0.42 (1.539)	4.56 (16.45)	0.32 (1.26)	3.34 (13.05)	0.04 (0.14)	2.52 (7.56)	BDL	1.12 (3.36)
recovery %	17.58	66.66	14.42	68.16	14.54	65.92	12.67	71.12
recovery	84.24		82.58		80.46		83.79	

[a] Numbers in parentheses indicate total milligrams recovered; P, parent; M, metabolite in terms of parent compound; BDL, below detection limit (<0.1).

Likewise, except lung, adrenal gland, ovary, testis, and mammary gland, all of the tissues retained the residue of the metabolite of metamitron in goats sacrificed on day 6. The quantities of metamitron and its metabolite recovered from tissues of goat on day 4 were highest, which then gradually declined along with days, and on day 7 no metamitron residue was recorded.

Gastrointestinal Tract Contents. Metamitron residue was below the detection limit in the rumen content, whereas the metabolite was recorded on days 4−7 in sequence. Maximum quantities of metamitron and its metabolite were recovered from small intestine content followed by large intestine content on days 4−7 in sequence (**Table 5**).

Total Recovery Percentage. Maximum percentages of parent and its metabolite in terms of parent compound were recovered from urine samples. Total recovery percentages from feces, gastrointestinal contents, urine, and tissues for metamitron and its metabolite in terms of parent compound from groups of goats on days 4, 5, 6, and 7 after dosing were 84.24, 82.58, 80.46, and 83.79 respectively (**Table 6**).

DISCUSSION

The absorption rate constant (K_a) value of metamitron was high, suggesting that the compound was rapidly absorbed from the gastrointestinal tract of goats. Accordingly, both metamitron and its metabolite [3-methyl-6-phenyl-1,2,4-triazin-5(4H)-one] could be detected in the blood of goats at 0.08 h. Elimination half-life of metabolite ($t_{1/2K}{}^{m}$) was 10 times greater than that of the parent compound, but the total body clearance (Cl_B) value of metamitron was 15 times greater than that of the body clearance ($Cl_B{}^{m}$) value of the metabolite. Maximum concentrations of metamitron and its metabolite were achieved in the blood of goat at 1 and 6 h, respectively, whereas the parent and its metabolite were retained in the blood for up to 12 and 96 h after administration, respectively. The higher elimination half-life coupled with the poor body clearance value of the metabolite justified the long persistence of the metabolite in blood.

Metamitron and its metabolite were excreted through feces for up to 48 and 168 h after administration, respectively. The percentage of recovery of the metabolite in terms of the parent

compound against the administered dose was 24 times greater than that of the parent compound. The recovery percentage of metamitron including metabolite in terms of the parent compound from feces varied from 21.5 to 33, of which the metabolite contributed 96%. Likewise, the parent compound and its metabolite were excreted through urine for up to 72 and 144 h, respectively. The percentage of recovery of the metabolite in terms of the parent compound from urine samples against the administered dose was 2.00 times greater than that of the parent compound. The recovery percentage of metamitron and its metabolite from urine varied from 38 to 42, of which the metabolite contributed >67%. Small intestine content retained the maximum amount of metabolite residue followed by large intestine and rumen contents of goats sacrificed on days 4, 5, 6, and 7. The volume of distribution of the metabolite (V^m) was 1.43 times lower than that apparent volume of distribution value ($V_{d,area}$) of the parent, suggesting limited distribution of the metabolite of metamitron, but all of the tissues except ovary, testis, lung, and adrenal and mammary glands of goats retained the metabolite residue for up to 6 days after administration.

Kinetic behaviors of metamitron in blood after a single oral administration of minimum toxic and maximum nontoxic dose levels in goats resemble each other, and the difference lies with the time of minimum detection level of the herbicide. The rate of transfer of metamitron from peripheral tissue to blood in both studies is greater than that of transfer of the compound from the blood to peripheral tissues, suggesting little possibility of bioaccumulation. Furthermore, detection of the metabolite and parent compound in the 5 min blood sample coupled with the induction of cytochrome P_{450} content of liver tissue (*3*) indicates rapid metabolism of the parent compound. The recovery percentages of metamitron in tissues against the administered dose in both of the studies are very poor, although bone retains the residue for up to 6 days after administration and deserves further study. Because the metabolite is retained in the blood for a longer time compared to the parent, a toxicity study of the metabolite may be carried out to get a better perspective.

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