Indian Journal of Animal Sciences **86** (6): 673–675, June 2016/Short communication

Comparison of pharmacokinetic parameters of oxytetracycline following single intravenous administration in goat, sheep and cattle calf

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Received: 29 March 2015; Accepted: 28 September 2015

Key words: Cattle calf, Dosages regimens, Goat, Oxytetracycline, Pharmacokinetics, Sheep

Pharmacokinetic studies provide the data necessary for calculating the dose and dosage regimen (Prescott and Baggot 1993). Tetracyclines are broad spectrum antibiotics with bacteriostatic activity against gram-positive and gram-negative bacteria, (Presscot and Baggot 1993). Presently, oxytetracycline is widely used for the treatment of bacterial infection in animals including aquaculture fish species, because of its broad spectrum of activity, low toxicity and capacity for diffusion into most body fluids and tissues. Information is available regarding pharmacokinetics of intravenous (i.v.) administered oxytetracycline in exotic breed of horses, lambs, dogs etc., however, a very meager information is available on pharmacokinetics of oxytetracycline in indigenous species of cattle, sheep and goat in Indian climatic condition. In veterinary medicine the choice of drug is limited due to the cost of therapy involved. Therefore, the present study was designed for evaluation of pharmacokinetics of oxytetracycline following single intravenous administration in calves, goat and sheep, and calculates the suitable dosages regimens.

Animals: For comparative pharmacokinetic studies of oxytetracycline in cattle- calves, sheep and goats, 15 animals were used 5 of each, male cattle-calves of age 1–1.5 years and weight 225–230 kg, male sheep of age 1.5–2.5 years and weight 15–16 kg and female goats of age 1–1.5 years and weight 12–13 kg, respectively. These animals were housed in animal house and kept on pre-experimental period of 1 month before the commencement of experiment to acclimatize them to the new environment. Proper physical and clinical examination was done before the start of experiment. The animals were kept on *ad lib.* stall- feeding of green fodder supplemented with concentrate ration and partial grazing. The animals had free access to clean drinking water. All the animals were dewormed with albendazole @ 5 mg/kg body wt., a fortnight before the experiment. The plan of work has been approved by the university ethical committee.

Chemicals: Oxytetracycline hydrochloride injectable solution (50 mg/ml) was used for pharmacokinetics study.

Drug administration and blood sampling: Oxytetracycline hydrochloride solution was injected as a single dose (5 mg/kg) intravenous (i.v.) bolus administration. An intervening wash out period of 4 weeks was given to all 5 calves. Prior to drug administration, a control blood sample was collected from each animal from the jugular vein in each heparinised tubes. The blood samples were collected from each animal in heparinized tubes through an i.v. canula placed in contralateral jugular vein at 0, 2, 5, 10, 15, 30, 60, 120, 240, 480, 720, and 1,440 min of post-medication. Plasma was separated and stored at –20 $^{\circ}$C till analyzed.

Extraction of oxytetracycline from plasma: Drug extraction from plasma sample was carried out as per Tyczkowska and Aronson (1986) with slight modification.

Analysis of oxytetracycline: The analysis of plasma samples for oxytetracycline was done as described by (Tyczkowska and Aronson 1986) with an isocratic mobile phase consisted of 20% acetonitrile HPLC grade, 2% phosphoric acid and 78% deionised water HPLC grade. The flow rate of mobile phase was kept at 0.5 ml/min. Chromatography was performed at 25^{0} C with UV detection at 355 nm. The chromatogram was analyzed by 'Chromatopak'. Oxytetracycline was eluted as sharp symmetrical peak at approximately 4.69 min.

HPLC conditions: Drug estimation in plasma was done by high performance liquid chromatography. The HPLC system comprised double plunger pump, rheodyne manual loop injector with a 20 µl loop and UV-VIS detector. Separation was achieved using C_{18} reverse phase column, particle size 5 µm (4× 150 mm) as a stationary phase.

Pharmacokinetic analysis: The pharmacokinetic analysis of the data obtained following i.v. administration in this study was done by employing pharmacokinetic software "PK Solution 2.0".

Dosages regimens: Regimens for oxytetracycline were

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Table 1. Pharmacokinetic parameters of oxytetracycline in plasma following single dose (5 mg/kg) i.v. administration in goat, sheep and calves (5)

Parameters	Unit	Mean ± SE		
		Goat	Sheep	Cattle Calves
A	µg/ml	3.44 ± 0.51	2.636 ± 0.57	6.41± 2.10
B	µg/ml	0.70 ± 0.15	0.699 ± 0.16	1.40 ± 0.27
α	min^{-1}	0.02 ± 0.00	0.014 ± 0.00	0.02 ± 0.00
β	min^{-1}	0.00066 ± 0.00	0.00096 ± 0.00	0.0010 ± 0.00
$t_{1/2\ \alpha}$	min	31.10 ± 2.69	56.214 ± 11.93	37.02 ± 9.51
$t_{1/2\ ß}$	min	1055.94 ± 133.82	597.834 ± 92.99	747.82 ± 160.39
AUC	µg/min/ml	1391.22 ± 145.02	1678.24 ± 557.60	2057.74 ± 244.72
MRT	min	1063.24 ± 131.66	545.94 ± 75.40	1143.28 ± 166.31
$V_{d\ (area)}$	ml/kg	5868.20 ± 1212.18	5436.44 ± 909.86	3428.32 ± 561.62
Vd_{ss}	ml/kg	4080.16 ± 813.48	3356.58 ± 998.95	2866.56 ± 440.25
Cl_b	ml/min/kg	3.75 ± 0.37	4.454 ± 0.20	2.57± 0.32

computed by the method described by Banet and collegues (1990).

The mean plasma drug concentration-time profile following single dose 5 mg/kg i.v. administration of oxytetracycline in goat, sheep and calves best described by two compartment model are presented in Table 1. The calculation of dosages regimen i.e. loading and maintenance dose based on single intravenous dose of 5 mg/kg was administered and plasma concentration of oxytetracycline was monitored.

The study showed that OTC maintained its minimum ETC of 0.5 µg/ml up to 480 min in goat and sheep, and 720 min in cattle calves after 5mg/kg body weight through intravenous administration, respectively. It suggested that drug is effective in systemic infection against the sensitive microorganism. The value of distribution rate constant were found in goat, sheep and calve respectively is less than the finding of Ziv *et al.* (1974) in cow and ewe, Verma *et al*. (1983) in buffalo calf, Ames *et al*. (1983) in bull calf, and Jayachandran *et al*. (1994) in female buffalo. The high and low value of distribution half-life $t_{1/2}\beta$ in goat, sheep and caves, respectively, obtained in the present study indicated that the drug may be distributed in body tissues and fluids at a faster rate in sheep in caparison to goat and calves.

The value of elimination half-life ($t_{1/2}\beta$) in goat, sheep and calves, respectively, obtained in the present investigation indicated that the drug is eliminated slowly from the body. This finding is corroborated with the findings of Ames *et al*. (1983) in bull calves and Jayachandran *et al*. (1994) in female buffaloes.

A high Vd_{area} (ml/kg) in goat, sheep and calves ,respectively, obtained in the present study denoted that the drug penetrates well into different body fluids and tissues. This is supported with the findings of Yoder *et al*. (1954) in cow, Turel *et al.* (2005) in mohair goat and Jayachandran *et al*. (1994) in female buffaloes.

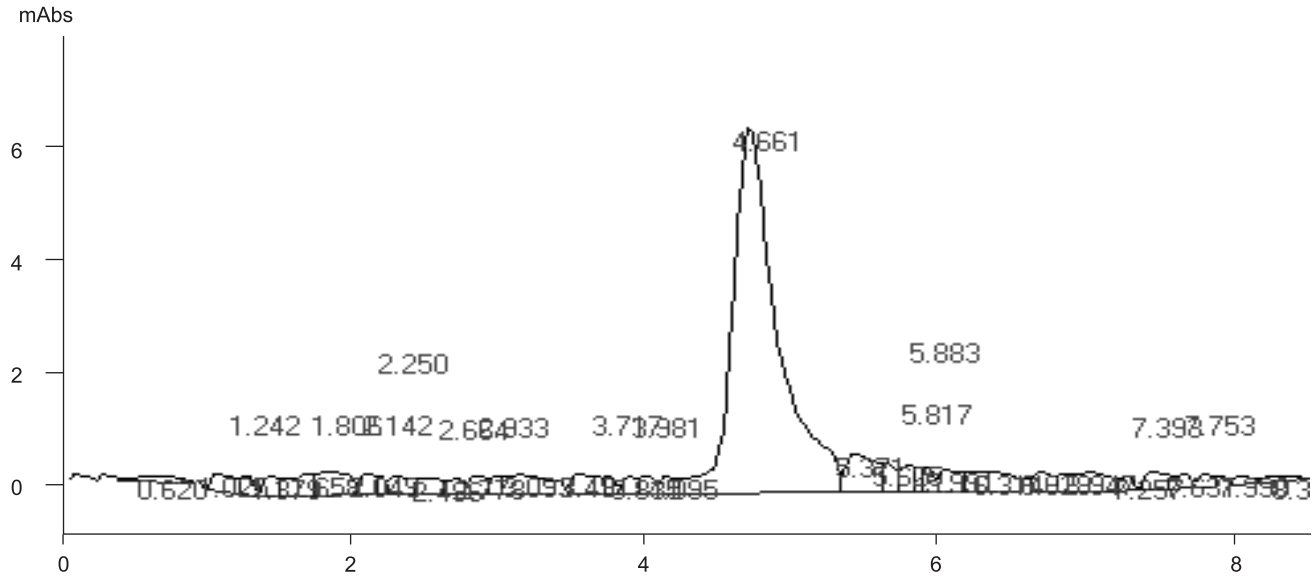

Fig.1. Chromatogram (HPLC) of oxytetracycline concentration using mobile phase acetonitrile (20%): phosphoric acid (2%): deionised water (78%).

The total area under curve (µg.min/mL) in this study was in agreement with the findings of Mandal *et al*. (1990). The parameter can be integrated with the MIC by calculating the extent of drug exposure (area) exceeding the MIC (AUC> MIC). The AUC> MIC parameter represent the amount of drug above the threshold for inhibition (Dudly 1991). In present study the AUC is sufficiently higher than the MIC (0.5 µg/ml) required for suppressing the growth of living organism.

MRT(mean residential time) in present study in goat, sheep and calves, respectively, were suggested that the slow rate of elimination of OTC from the body supported by the finding of Jayachandran *et al*. (1994) in female buffalo.

On the basis of this pharmacokinetic study, the dosage regimen was suggested as 3.43 (mg/kg) as priming doses and 0.5 (mg/kg) as maintenance doses following i.v.. administration, respectively, at 360 min interval in goats and for sheep is proposed as 3.75 mg/kg as priming doses and 1.10 mg/kg as maintenance dose following i.v. administration, respectively, at 360 min interval. The doses regimen in this study was calculated as 3.52 mg/kg as priming dose followed by 1.80 mg/kg as maintenance dose at 720 min following i.v. in cattle calves.

SUMMARY

The study was conducted to evaluate pharmacokinetics of oxytetracycline following single intravenous administration in goat sheep and cattle calves, and calculate the suitable dosages regimens. For this 15 animals were used 5 each of female goats, male sheep and male cattle calves in each species. Oxytetracycline hydrochloride solution was injected as a single dose (5 mg/kg) intravenous (i.v.) bolus administration. The analysis of plasma samples for oxytetracycline was done by HPLC. The OTC maintained its minimum ETC of 0.5 µg/ml up to 480 min in goat and sheep and 720 min in cattle calves after 5mg/kg body weight through intravenous administration, respectively. The pharmacokinetic parameters obtained in this study indicates that the OTC have wide distribution and longer residential time in body and maintained the therapeutic concentration in body.

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