PHARMACOKINETICS AND URINARY EXCRETION OF PARACETAMOL FOLLOWING INTRAVENOUS ADMINISTRATION IN BUFFALO CALVES

Mukesh Kumar, Sushma Lalita Baxla, S.D. Singh and C. Jayachandran
Department of Pharmacology and Toxicology, Bihar Veterinary College, Patna - 800 014, India

ABSTRACT
Pharmacokinetic study of paracetamol was conducted in five female buffalo calves following single i.v. injection of paracetamol @ 40 mg/kg. The drug was detected up to 2 h only in plasma, while it was detected for a longer period of 48 h in urine with a mean concentration of 1.87 ± 0.48 and 10.90 ± 1.14 mg/ml, respectively. The mean distribution half life (t1/2α) of 0.11 ± 0.01 h and elimination half life (t1/2β) of 0.77 ± 0.09 h indicated that the drug is rapidly distributed as well as eliminated quickly in buffalo calves. The rapid elimination of the drug is due to the higher values of rate constant of drug elimination from central compartment (Kel) of 1.471 ± 0.089 h⁻¹ and total body clearance (ClB) of 43.67 ± 3.39 ml/kg/min. This led to the lower value of mean residential time (MRT) of 1.00 ± 0.01 h, indicating that paracetamol remained for a shorter period only in the body of buffalo calves. A higher Vdarea of 2.34 ± 0.19 L/kg obtained in the present study suggested good distribution of paracetamol in body fluids and tissues which is further supported by the approximate tissue to plasma concentration ratio (T/P) of 0.59 ± 0.13.

INTRODUCTION
Paracetamol, a member of nonsteroidal antiinflammatory drugs (NSAIDs) possesses strong antipyretic and analgesic actions and popularly used in human medicine as well as in veterinary medicine. It is a suitable substitute for aspirin as analgesic or antipyretic in whom aspirin is contraindicated (e.g., patients with peptic ulcer) or those patients who had prolonged bleeding time caused by aspirin. It is a weak inhibitor of cyclo-oxygenase in the presence of high concentrations of peroxides that are found in inflammatory lesions and hence, fails to exert antiinflammatory action (Marshal et al., 1987). Like other NSAIDs, paracetamol does not inhibit the neutrophil activation (Abramza and Weissmann, 1989). As analgesic and antipyretic, paracetamol is superior to many NSAIDs and hence, it is highly popular and useful in human medicine as well as in animal practices also. The present investigation was therefore carried out in buffalo calves, the chief milk yielding species of Indian sub continent.

MATERIAL AND METHODS
In the present study, five clinically healthy female buffalo calves of non-descript breed aged 12-18 months and weighing 105 - 180 kg body weight were used. Paracetamol (Parectol - Vet® 15%, Sarabhai Zydus Animal Health Limited, India) was injected intravenously @ 40 mg/kg through jugular vein in each buffalo calf. Blood samples were collected from contra lateral jugular vein in sterilized centrifuge tubes containing appropriate amount of sodium oxalate. Plasma was separated by centrifugation at 2500 r.p.m. for 10 to 15 min. For collection of urine, a sterile Foley’s balloon catheter (No 12) was introduced through urethra and kept in position by inflating the balloon with 20 ml of water. Urine samples were also collected in sterilized test tubes. The biological samples (blood and urine) were collected before and at 0.042, 0.083, 0.167, 0.25, 0.333, 0.50, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 24 h post i.v. injection of the drug. Urine samples were further collected even beyond 24 h at 30, 36 and 48 h. The biological fluids collected before injection were used for preparing standards in the respective biological fluid. The collected biological samples and their standards were
kept under refrigeration and were analyzed within three days of collection.

The concentrations of paracetamol in plasma and urine were estimated by spectrophotometric method (Archer and Richardson, 1980; Omar and Mohammad, 1984). Pharmacokinetic parameters were calculated after i.v. administration from log plasma drug concentration versus time curve. Since the log plasma drug concentration versus time profile showed biphasic pattern, kinetic parameters were derived from formulae of 2-compartment open model by using least square regression method (Gibaldi and Perrier, 1982; Notari, 1980).

RESULTS AND DISCUSSION

Fig. 1 depicts the concentrations of paracetamol in biological fluids (plasma and urine) of buffalo calves following its i.v. injection @ 40 mg/kg. The drug was detected up to 2 h only in plasma, while it was detected for a longer period of 48 h in urine with mean values of 1.87 ± 0.48 and 10.90 ± 1.14 mg/ml, respectively. The mean peak urine concentration of 2022 118.8 mg/ml was attained at 1.5 h.

Various pharmacokinetic parameters, which describe the distribution and elimination of paracetamol in buffalo calves are presented in Table 1. The distribution rate constant (a) of 7.148 ± 1.361 h⁻¹ and distribution half life (t₁/₂α) of 0.11 ± 0.01 h obtained for paracetamol in the present study denote that drug is rapidly distributed in buffalo calves. Similar value of t₁/₂α has been reported by Manna et al. (1994) in Black Bengal goat (0.10 h),

![Graph showing concentrations of paracetamol in plasma and urine of buffalo calves after a single i.v. dose (40 mg/kg)](image)

**Fig. 1.** Concentrations of paracetamol in plasma and urine of buffalo calves after a single i.v. dose (40 mg/kg)
Table 1. Various Pharmacokinetic parameters of paracetamol after single i.v. dose of 40 mg/kg in buffalo calves (n=5)

<table>
<thead>
<tr>
<th>Kinetic parameter (Unit)</th>
<th>Value (Mean±S.E.M.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (µg/ml)</td>
<td>9.51 ± 1.94</td>
</tr>
<tr>
<td>B (µg/ml)</td>
<td>13.11 ± 1.08</td>
</tr>
<tr>
<td>C0 = (mg/ml)</td>
<td>22.62 ± 1.08</td>
</tr>
<tr>
<td>α (h⁻¹)</td>
<td>7.148 ± 1.361</td>
</tr>
<tr>
<td>β (h⁻¹)</td>
<td>0.965 ± 0.136</td>
</tr>
<tr>
<td>t1/2α (h)</td>
<td>0.11 ± 0.01</td>
</tr>
<tr>
<td>t1/2β (h)</td>
<td>0.77 ± 0.09</td>
</tr>
<tr>
<td>K12 (h⁻¹)</td>
<td>1.672 ± 0.142</td>
</tr>
<tr>
<td>K21 (h⁻¹)</td>
<td>4.970 ± 1.540</td>
</tr>
<tr>
<td>Kel (h⁻¹)</td>
<td>1.471 ± 0.089</td>
</tr>
<tr>
<td>AUC (mg/L·h)</td>
<td>15.09 ± 2.56</td>
</tr>
<tr>
<td>MRT (h)</td>
<td>1.00 ± 0.10</td>
</tr>
<tr>
<td>T/P</td>
<td>0.65 ± 0.06</td>
</tr>
<tr>
<td>Vdarea (L/kg)</td>
<td>2.79 ± 0.14</td>
</tr>
<tr>
<td>ClB (ml/kg/min)</td>
<td>43.67 ± 3.39</td>
</tr>
</tbody>
</table>

A = Zero time distribution concentration; 
B = Zero time elimination concentration; 
C0 = Theoretical zero time concentration (A+B); 
α = Absorption rate constant; 
β = Elimination rate constant; 
t1/2α = Distribution half life; 
t1/2β = Elimination half life; 
K12 = Rate constant of drug transfer from central compartment to peripheral compartment; 
K21 = Rate constant of drug transfer from peripheral to central compartment; 
Kel = Rate constant of drug elimination from central compartment; 
AUC = Total area under the plasma drug concentration curve; 
AUMC = Area under first moment curve; 
MRT = Mean residential time; 
T/P = Fraction of drug available for elimination from central compartment; 
Vdarea = Apparent volume of distribution; 
ClB = Total body clearance.

while higher value of t1/2α (0.24 ± 0.04 h) in lactating goat has been reported by Sudha Kumari (1998).

The elimination rate constant (β) and elimination half life (t1/2β) of paracetamol were 0.965 ± 0.136 and 0.77 ± 0.09 h, respectively. Similar value of t1/2β was obtained by Manna et al. (1994) in Black Bengal goat (0.53 h). Comparatively, higher t1/2β values were reported by Sidhu et al. (1993) in buffalo calf (8.69 ± 0.83 h), Sharma et al. (1995) in cross bred calf (4.84 ± 1.26 h) and Sudha Kumari (1998) in lactating goat (3.56 ± 0.13 h). The lower t1/2β obtained in the present study denotes that the drug is eliminated at a faster rate from the body of buffalo calves, which is further supported by higher values of rate constant of drug elimination from the central compartment (Kel) of 1.471 ± 0.089 h⁻¹ and total body clearance (ClB) of 43.67 ± 3.39 ml/kg/min. This led to the lower value of mean residential time (MRT) of 1.00 ± 0.10 h. As compared to the ClB values observed in the present study, high ClB values of 113 ± 39.8 ml/kg/min in buffalo calf (Sidhu et al., 1993), 79.6 ± 22.7 ml/kg/min in cross bred...
calf (Sharma et al., 1985) and 17.37 ± 1.46 ml/kg/min in goat (Sudha Kumari, 1998) were reported.

Volume distribution (Vd) of 2.79 ± 0.14 L/kg was obtained for paracetamol in the present study in buffalo calf after its iv. administration. A lower Vd of 1.22 ± 0.23 L/kg in buffalo calf (Sidhu et al., 1993) and very low Vd of 0.48 ± 0.11 L/kg in cross bred calf (Sharma et al., 1995) were reported following i.m. administration of paracetamol. However, higher Vd of 5.48 ± 1.40 L/kg was found in goat following i.v. injection (Sudha Kumari, 1998). Vd > 1 L/kg obtained in the present study for paracetamol denotes good distribution of the drug in body fluids and tissues of buffalo calf. This is further supported higher value of 0.59 ± 0.13 observed for the parameter, approximate tissue to plasma concentration ratio (T/P) in the present study for buffalo calf.

ACKNOWLEDGEMENT
The authors express their sincere gratitude to Rajendra Agricultural University, Bihar, Pusa, Samastipur for providing financial help and other facilities to carry out this investigation smoothly.

REFERENCES