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Effect of Acute Renal Failure on the Disposition Kinetics of Sparfloxacin in Goats

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ABSTRACT

Sparfloxacin is a third generation fluroquinolone derivative used as antimicrobial agent in human as well as in livestock. To establish proper dosage regimen in healthy as well as in acute renal failure condition in goat sparfloxacin was administered at a dose rate of 30 mg kg^{-1} body weight by intravenous route. Kidney was damaged experimentally by blocking urinary bladder and was assured by increased blood urea nitrogen and plasma creatinine level. The values of Cp_{max} and Cp_{min} of sparfloxacin in healthy goats were found to be 18.36 ± 0.52 and 0.66 ± 0.01 µg ml^{-1} at 0.08 and 10 hr respectively, while the respective values were 21.16 ± 0.44 and 0.53 ± 0.03 µg ml^{-1} at 0.08 and 14 hr in goats of acute renal failure. Pharmacokinetic parameters like B, t ½ β, AUC and MRT were higher in acute renal failure goats where as β and Cl_B values were decreased compared to healthy goats. Acute renal failure condition alters kinetic behavior of sparfloxacin in goats.

Keywords: Acute renal failure, goat, sparfloxacin, Disposition kinetics.

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INTRODUCTION

Sparfloxacin is a new generation commercially available quinolone antibacterial agent which is effectively used in various community acquired and nosocomial infection like respiratory tract, urinary tract and skin infection [1]. Sparfloxacin shows potent antimicrobial activity against wide range of gram positive and gram negative bacteria including glucose non fermentors and anaerobes, *Legionella* spp, *Mycoplasma* spp. *Chlamydia* spp, and *Mycobacteria* spp. Methicillin resistant *Staphylococcus aureus* is also susceptible to sparfloxacin [2]. The sporadic disease of pyelonephritis, embolic nephritis and nephrosis in farm animals have been reported which is caused by different type of bacteria like *Corynebacterium renale*, *Leptospira ponoma* and *Leptosira hardjo*, *Pseudomonas* spp, *Streptococcus* spp and *Staphylococcus* spp, Sparafloxacin has revealed excellent effect against these microorganism [3].

Renal impairment alters the normal disposition kinetics of some chemotherapeutic agent in animals [4]. Renal excretion is the primary route of elimination for quinolones [5]. Therefore, it is expected that renal impairment may result into a decreased renal clearance of these drugs. Literatures on disposition kinetics of sparfloxacin in healthy as well as kidney damaged goats are scarcely available. Goat is considered as one of the most important domestic farm animals in the world as a source of meat, milk and hide and plays a vital role in the agricultural economy of the small and marginal farmers and the landless labors of country. So Black Bengal goat was considered as test animal in present experiment.

Therefore, the present research work has been carried out to determine pharmacokinetics of sparfloxacin in goats of mechanically induced acute renal failure in order to utilize the data for the selection of dosage regimen.

MATERIALS AND METHODS

Animals

Twelve clinically healthy Black Bengal female goats weighing between 10 – 13 kg of 1-1 ½ year age were used in this experiment. The animals were kept in individual custom made stainless steel cage (size – 48□ × 48□ × 36□) in the temperature (22 ± 2°C) controlled room having provision of artificial light. The animals were dewormed with a single oral dose (7.5 mg/kg) of levamisole. After 21 days they were acclimatized with laboratory condition for 7 days. The animals were fed with standard ration consisting of 2 parts wheat husk, 1 part ground nut cake, 1 part crushed gram, 1 part crushed maize and 1 parts green. Water was provided ad libitum. [6] The lower part of neck of each animal was shaved to expose both the jugular veins. The animals were kept over night fasting prior to the start of experiment.

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Drugs and chemicals

Sparfloxacin analytical grade (Purity >98%) was supplied by M/S Alembic, India. All other chemicals used for the experiment were supplied by Rankem and E-Merk (India).

Experimental Design

Ten goats of either sex were divided into two equal groups. First group was served as healthy control where as goats of second group was induced acute renal failure by blocking of urinary bladder using Foley's catheter. A single dose of Sparfloxacin dissolved in three mille litter of formal glycerol was administered intravenously to all goats of both groups at a dose rate of 30 mg/kg body weight.

Induction of acute renal failure

Acute renal failure in goats of group II was induced by blocking the urinary bladder using Foley's catheter. After blocking of the urinary bladder, the increased urine volume in urinary baldder created a negative pressure on kidney resulting in acute renal failure. The intensity of acute renal impairment was assessed by estimation of Blood urea Nitrogen (BUN) and Blood creatinine levels at different time interval. The catheter was removed when the level of BUN and cretinine were increased 4-5 fold than the normal value. Sparfloxacin was administered for kinetic study after 6 hr of removal of catheter.

Collection of blood samples

Blood samples were collected from Jugular vein in heparinized test tube at 0, 0.08, 0.16, 0.33, 0.50, 0.66, 1, 2, 3, 6, 8, 10, 12 and 14 hrs after sparfloxacin administration. About 2.0 ml of blood was collected at the above mentioned time and plasma was then separated by centrifugation at 3000 rpm for 30 min. One ml of plasma was utilized for analysis of sparfloxacin.

Analytical method

Estimation of sparfloxacin in plasma

To a test tube, 0.5 ml of plasma was mixed with, 4.5 ml of acetonitrile and shaked vigorously for 4 min. It was then centrifuged at 3000 rpm for 15 min. The supernatant was collected and absorbance was read in double beam UV-VIS spectrophotometer (Chemito 2600) at 301 nm wavelength against blank prepared with plasma collected at '0' hr. concentration of sparfloxacin present in each blood sample was then calculated from standard curved prepared earlier and expressed as $\mu g\ ml^{-1}$. [7]

Recovery of sparfloxacin from plasma

Recovery of sparfloxacin from goat plasma was carried out *in-vitro* to ascertain the reliability of analytical method after fortifying0.25, 0.5, 1, 2, 4, 5, 8 and10 μg ml^{-1} of Sparfloxacin (analytical grade). The absorbance maximum of sparfloxacin was found to be at 301 nm. The absorbance against several concentration of sparfloxacin at 301 nm was plotted on graph paper and linearity was found to be maintained. The recovery was 85-90% and therefore analytical method was considered for estimation of sparfloxacin in this experiment. The limit of detection of sparfloxacin was 0.4 μg ml^{-1}.

Blood Chemistry

Estimation of BUN

Blood urea nitrogen level was estimated by diacetyl monooxime method described by Wooton, et al [8].

Estimation of creatinine

The plasma creatinine level was estimated by the Jaffes reaction method as described by Wooton, et al [9].

Pharmacokinetic parameters

Pharmacokinetic parameters of sparfloxacin were determined from computerized curve fitting programme 'PHARMKIT' supplied by Deptt. Of pharmacology, JIPMER, Pondicherry, India. Dosage regimen of sparfloxacin was done by standard method of Rowland et al, 1980. [10]

Statistical analysis

The data were analysed for statistical significance by student't' test.

RESULTS

Mechanically Induced Acute Renal Failure

Blood Urea Nitrogen

BUN levels of normal healthy goats of group I showed non-significant differences while increased BUN level was observed in group II goats after 36 hr onwards. The level of BUN was increased four folds in goats of group II compared to group I at 60 hr. (Fig. 2)

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Plasma creatinine

No significant changes in plasma creatinine level with respect to 0 hr. at different time intervals in animals of group I were observed where as significant changes in CRT values started to increase from 36 hr, and increased about 4.5 folds at 60hr compared to 0 hr in group II. (Fig. 3)

Pharmacokinetics

The maximum and minimum plasma concentrations of sparfloxacin found in healthy (group I) goats were 19.36 ±0.52 and 0.66 ±0.12 μg ml^{-1} at 0.08 and 10 hr respectively. It is further evident from (Fig. 1) that plasma concentration of sparfloxacin remained significantly higher in group II goats from 0.08 to 0.33 hr and from 6hr. onwards. Figure. 1 reveals that the concentration of sparfloxacin in plasma decreased rapidly till 1 hr which was followed by gradual decrease in concentration till 10 hr in healthy goats (group I) and sparfloxacin could not be detected beyond 10 hr post administration. A like trend in concentration of sparfloxacin was found in group II goats but the drug persisted till 14 hr. The mean pharmacokinetic parameters of sparfloxacin have been presented in table. 1. Significant higher value of t ½ β and lower value of Cl_B in group II goats suggest slow elimination of drug in acute renal failure goats. The value of AUC and MRT of sparfloxacin in group II goats increased significantly compared to healthy group while goats of both groups show wide distribution.

Based on relevant pharmacokinetic parameters derived from the respective plasma concentration time profile, the rational dosage regimens for sparfloxacin in healthy and acute renal failure condition goats have been formulated and presented in table. 2.

DISCUSSION

Renal failure is manifested by the clinical state of uremia which can also occur in urinary tract obstruction [11]. Uremia is a toxaemic syndrome resulting from renal insufficiency. It is partly due to retention and toxic action by non protein nitrogenous substances including urea, creatinine, amino acid, uric acid, ammonia etc [12]. Therefore the higher values of urea and creatinine in plasma of goats by blocking of urinary bladder in present experiment may cause acute renal failure. Sastry, G.A. [12] reported that glomerular filtration rate decreased in uremia. Most of the fluroquinolones are eliminated primarily through glomerular filtration and tubular secretion in the kidney. Probenecid did not alter pharmacokinetics of sparfloxacin suggesting excretion of sparfloxacin through glomerular filtration not via tubular secretion. Hence the decrease value of Cl_B of sparfloxacin in group II goats might be due to reduced glomerular filtration as evidenced in uremic condition. It has been reported that most of the sensitive and variable sensitive micro organism are inhibited with the range of 1 to 4 μg ml^{-1}. In view this following dosage regimen would be expected to be effective in combination diseases caused by sensitive microorganism in goats. Finally it can be conclude that the pharmacokinetic profiles of sparfloxacin were altered in acute renal failure condition in goats.

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Table 1. Pharmacokinetic parameters of sparfloxacin after single dose intravenous administration @ 30 mg kg^{-1} to both groups

Parameters	Control (group I)	Acute renal failure (group II)
B ($\mu g\ ml^{-1}$)	17.60±1.11	18.36±0.21
β (hr^{-1})	0.32±0.01	0.25*±0.06
t ½ β (hr)	2.17±0.11	2.72*±0.06
Vd_{area} ($L\ kg^{-1}$)	1.63±0.10	1.67±0.02
Vd_c ($L\ kg^{-1}$)	1.73±0.11	1.63±0.02
AUC ($\mu g\ hr\ L^{-1}$)	56.00±0.86	68.34*±1.44
AUMC ($\mu g\ hr^2 L^{-1}$)	159.96±6.50	242.19*±8.08
MRT (hr)	3.13±0.16	3.94*±0.10
Cl_B (hr)	0.52±0.01	0.42*±0.01

* Indicates values were significant at P<0.05.

Abbreviation: B, Zero time plasma sparfloxacin concentration of biphasic intravenous disposition curve; β, Elimination rate constant; t ½ β, Elimination half life; Vd_{area}, Apparent volume of distribution; Vd_c, Apparent volume of distribution in central compartment; AUC, Area under curve; AUMC; Area under the first moment time curve; MRT, Mean residence time; Cl_B, Total body clearance.

Table 2. Dosage regimens for sparfloxacin in healthy and acute renal failure condition of goats for intravenous administration.

Groups	Dose ($mg\ kg^{-1}$)		Dose interval (hr)
	LD	MD	
Group I	25.51	19.16	4.34
Group II	54.67	40.62	5.44

LD = Loading Dose
MD = Maintenance Dose

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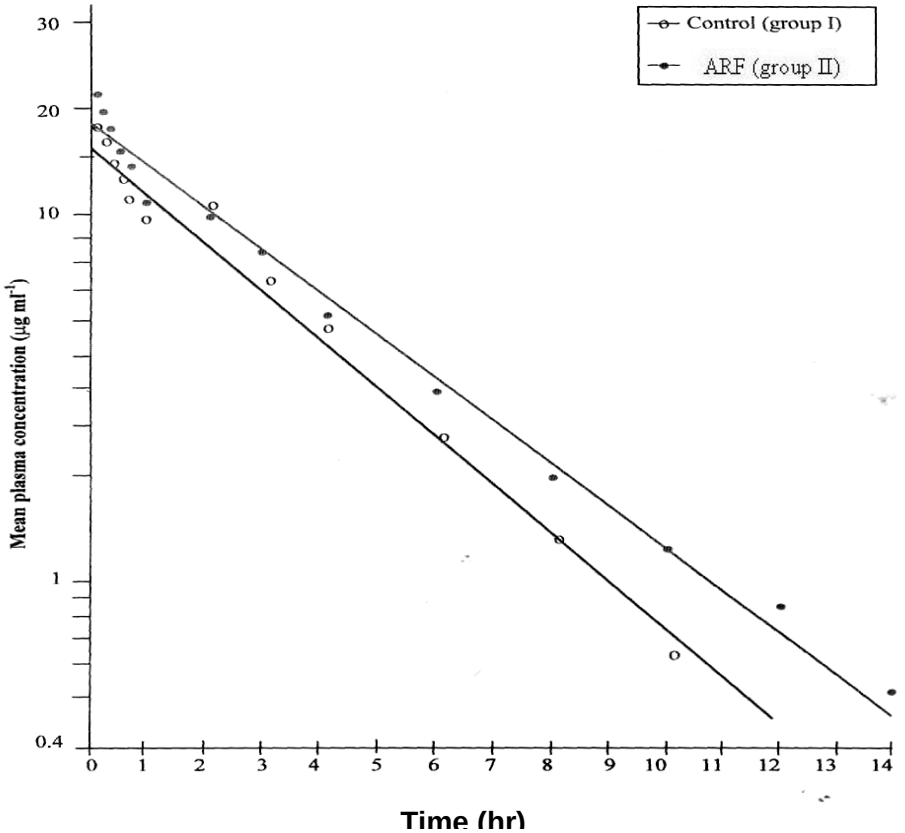

Figure 1. Semilogarithmic plots of mean plasma concentration of Sparfloxacin against time with computerized best-fit-line after single intravenous administration at 30 mg kg $^{-1}$ in healthy and acute renal failure goats.

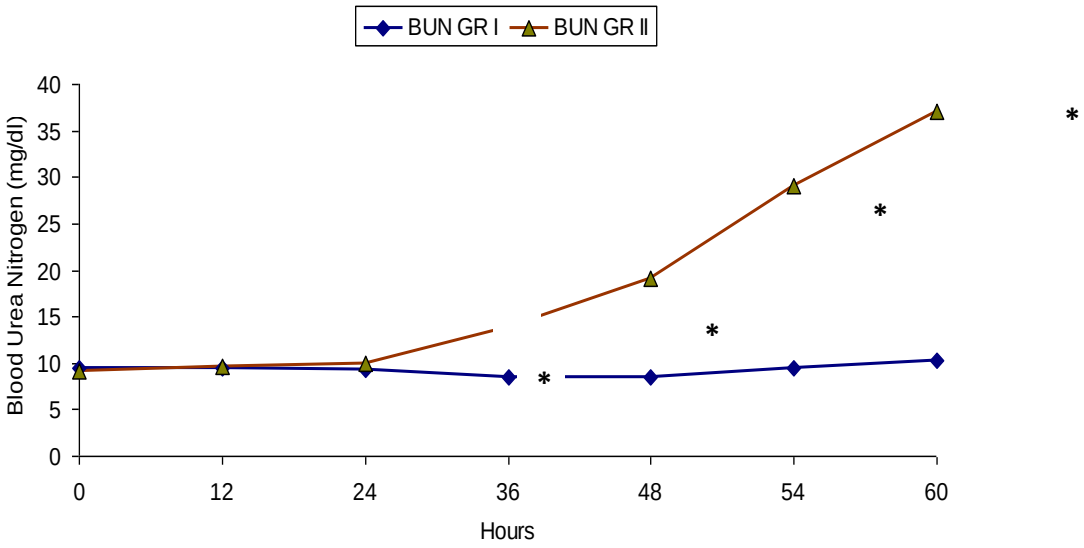

Figure 2. Blood Urea nitrogen levels at different time intervals in goats following blocking of urinary bladder.
* Indicates values were significant at P<0.05.

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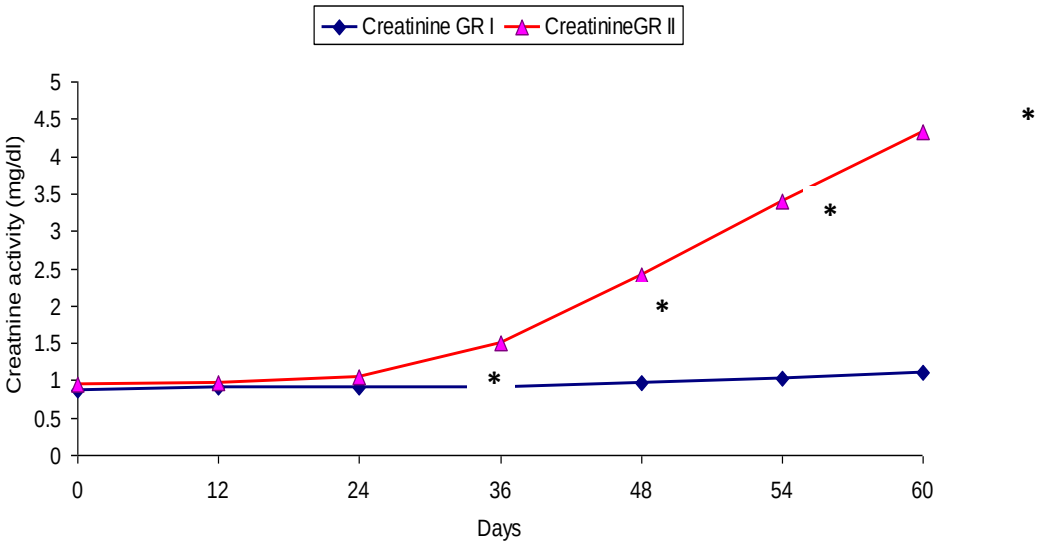

Figure 3. Plasma Creatinine levels at different time intervals in goats following blocking of urinary bladder.
* Indicates values were significant at P<0.05.

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