IJMPR 2020, 4(6), 127-131

International Journal of Modern Pharmaceutical Research

www.ijmpronline.com

ISSN: 2319-5878
IJMPR
Research Article

SJIF Impact Factor: 5.273

DISPOSITION KINETICS OF CEFTRIAXONE AND TAZOBACTAM IN BROILER, RHODE ISLAND RED AND HARINGHATA BLACK POULTRY FOLLOWING SINGLE DOSE INTRAMUSCULAR ADMINISTRATION

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Received on: 09/11/2020
Revised on: 30/11/2020
Accepted on: 21/12/2020

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ABSTRACT

Background: The Extended spectrum β lactamases (ESBLs) producing organisms are highly prevalent in poultry and poultry products. These ESBLs producing bacteria can hydrolyze β lactam antibiotics (like ceftriaxone, cefotaxime) which may result in treatment failure and development of antimicrobial resistant. **Objective:** The study was conducted to evaluate the disposition kinetics of ceftriaxone (3rd generation cephalosporin) and tazobactam (beta-lactamase inhibitor) in broiler, Rhode Island Red and Haringhata black poultry following single dose intramuscular administration and to evaluate the possible use of ceftriaxone- tazobactam combination (8:1) for treating resistant bacterial infections in poultry. **Method:** A single dose of ceftriaxone @ 25 mg kg^{-1} and tazobactam @ 3.125 mg kg^{-1} was administered intramuscularly to eighteen poultry (six poultry each in broiler, Rhode Island Red and Haringhata black breed) and blood samples were collected at predetermined time interval for HPLC analysis. **Result:** Both ceftriaxone and tazobactam persisted up to 6 h in plasma of all three breeds of poultry without showing significant inter-breed variations. The plasma concentration of ceftriaxone maintained above the minimum inhibitory concentration of 0.12 µg mL^{-1} required against TEM-1 containing *Escherichia coli***.** The pharmacokinetic study revealed that both ceftriaxone and tazobactam was absorbed quickly from intramuscular absorption site with significant volume of distribution in all three breeds of poultry. The plasma concentration also maintained a 8:1 ratio for ceftriaxone and tazobactam. **Conclusion:** Therefore ceftriaxone @ 25 mg kg^{-1} and tazobactam @ 3.125 mg kg^{-1} may effectively be used as 8:1 combination to treat ESBL producing bacterial infection in poultry.

KEYWORD: Ceftriaxone, Tazobactam, Disposition Kinetics, Poultry.

INTRODUCTION

Ceftriaxone is a broad spectrum third generation cephalosporin with potent activity against gram positive and gram negative bacteria including Enterobacteriaceae, *Heamophilus influenza*, *Streptococcus pneumonia* and other non-enterococcal streptococci.[1] But extended spectrum β lactamases (ESBLs) producing bacteria can hydrolyze β lactam antibiotics which contain an oxyimino group (e.g. ceftazidime, ceftriaxone, cefotaxime or aztreonam) and pose a great threat to public health in terms of treatment failure and antibiotic resistance development. Tazobactam is a penicillinic acid sulfone that inhibits a variety of plasmid-mediated β lactamases, especially those belonging to the SHV-1 and TEM groups. Broilers are the most commonly reared poultry for meat purpose and Rhode Island Red is a backyard dual purpose poultry reared for its egg laying capacity and hardiness. Whereas, Haringhata black is an indigenous breed of poultry found in northern parts of North 24 Paragana and southern parts of Nadia district of West Bengal, India. ESBL producing organisms are highly prevalent in poultry and poultry products with CTX-M-1, TEM-52 and SHV-12 being the most common type of ESBLs.[2] These ESBLs were commonly found in *Klebsiella pneumoniae*, but presently being also found in *Escherichia coli*, *Proteus mirabilis* and other bacteria under Enterobacteriaceae.[3,4] Samanta et al. (2014) also reported isolation of ESBL containing *E. coli* from backyard poultry birds in West Bengal, India.[5] As per reports the minimum inhibitory concentration (MIC) of ceftriaxone was ≤ 0.12 µg mL^{-1} against inoculums of 10^5 and 10^6 c.f.u. mL^{-1} of TEM-1 containing *Escherichia coli*.[6] Ceftriaxone and tazobactam combination is commercially available at 8:1 ratio for treatment of various bacterial infections. So, this ceftriaxone-tazobactam combination (8:1) can be effective therapy to treat ESBLs producing bacterial infection in poultry as tazobactam can prevent breakdown of ceftriaxone by ESBL producing bacteria and thereby to prevent antimicrobial resistance development. A study showed that ceftriaxone-sulbactam

combination is more effective than ceftriaxone alone for prevention of mutation in ESBL producing organisms in vitro with MPC (mutation prevention concentration) of >256 µg mL^{-1} for ceftriaxone-sulbactam combination and >512 µg mL^{-1} for ceftriaxone alone.[7] But, tazobactam was reported to show significantly greater activity than sulbactam towards inhibition of β lactamases.[8] Therefore present experiment was conducted to study disposition kinetics of ceftriaxone @ 25 mg kg^{-1} and tazobactam @ 3.125 mg kg^{-1} in broiler, Rhode Island Red and Haringhata black poultry following single intramuscular administration for finding the possible therapeutic application of ceftriaxone-tazobactam (8:1) combination for treating ESBL producing organism infections in poultry.

MATERIALS AND METHODS

For the experiment, analytical grade ceftriaxone sodium and tazobactam sodium (purity ≥ 95 %) were procured from Alembic Limited, Mumbai, India and Sigma Aldrich, respectively and all other chemicals were obtained from E. Merck (India) and Sigma Chemicals Co., USA.

Eighteen clinically healthy adult poultry (six poultry each in broiler, Rhode Island Red and Haringhata black breed) were procured from Instructional poultry farm, West Bengal University of Animal and Fishery Sciences, Kolkata, India. All the poultry were quarantined for a period of 14 days before commencement of the experiment. The broilers were 30 days old and the Rhode Island Red and Haringhata black poultry were approximately 12 weeks old. They were caged individually and provided with commercial feed and potable drinking water *ad libitum*. A single dose of ceftriaxone @ 25 mg kg^{-1} was administered intramuscularly to all eighteen poultry (six poultry each in broiler, Rhode Island Red and Haringhata black breed) and blood samples (2 mL) were collected from the collateral wing vein in heparinized test tubes at 0 (pre dosing), 0.04, 0.08, 0.25, 0.5, 0.45, 1, 2, 4, 6, 8 h post dosing (pd). A single dose of tazobactam @ 3.125 mg kg^{-1} was administered intramuscularly to the same eighteen poultry after allowing 10 days wash out period for studying the disposition kinetics of tazobactam. Blood samples (2 mL) were collected at predetermined time interval of 0 (pre dosing), 0.08, 0.25, 0.5, 0.45, 1, 2, 4, 6, 8, and 12 h pd. Plasma was then separated by centrifugation at 3000 rpm for 20 min and stored at 4˚C for high performance liquid chromatography (HPLC) analysis. All the experimental procedures were conducted as per the guidelines of the Institutional Animal Ethics Committee (IAEC), West Bengal University of Animal and Fishery Sciences, dated 09.03.2011.

SHIMANDZU LC-20 AT liquid chromatograph coupled with Photo Diode-Array (PDA) detector attached with computer SPD-MXA 10 software was used for analysis of the drugs. The mobile phase was prepared as per the method mentioned in the USP. The HPLC apparatus has 5µ Luna C18 (2); 250 × 4.6 mm (RP) column. Ceftriaxone[9] and tazobactam[10,11] was extracted and estimated as per the reported methods. Standard and sample (20 µL) were injected by Hamilton syringe into the injector port of HPLC and a flow rate of 1.5 mL min^{-1} was maintained. Measurements were performed at a wavelength of 254 nm for ceftriaxone and 210 nm for tazobactam.

Pharmacokinetic parameters of ceftriaxone and tazobactam were determined from computerized curve fitting programme "PHARMKIT" supplied by the Department of Pharmacology, JIPMER, Puducherry, India. The data obtained from this programme were analysed for deriving some of the pharmacokinetic parameters as per standard formulae.[12] The data were expressed as mean ± standard error (S.E.) and analyzed statistically using t-test of IBM SPSS statistic, version 21, 2012.

RESULTS AND DISCUSSION

The recovery percentages of ceftriaxone and tazobactam from plasma were 81.14±4.95 % and 83.01±3.6 %, respectively. The limit of detection for both the drugs in plasma was 0.5 ppm (parts per million) and sensitivity was 0.25 ppm. The linearity of calibration curves was checked for both the drugs and linearity was found to be maintained in the range of 0.5 to 25 ppm for ceftriaxone and 0.5 to 10 ppm for tazobactam in plasma.

The mean plasma concentrations of ceftriaxone @ 25 mg kg^{-1} and tazobactam @ 3.125 mg kg^{-1} following single intramuscular administration in broiler, Rhode Island Red and Haringhata black poultry was depicted in figure 1 and figure 2 respectively. Ceftriaxone achieved a maximum plasma concentration of 26.07±0.47, 26.36±1.15 and 25.73±0.47 µg mL^{-1} respectively in broiler, Rhode Island Red and Haringhata black poultry at 0.08 h pd, which declined gradually and achieved a minimum plasma concentration (0.60±0.08, 0.55±0.09, 0.64±0.06 µg mL^{-1}, respectively) at 6 h pd. The plasma concentration of ceftriaxone was below detection level at 8 h pd in all three breeds of poultry. Tazobactam reached highest plasma concentration of 4.29±0.11, 4.21±0.20, 4.27±0.23 µg mL^{-1} respectively in broiler, Rhode Island Red and Haringhata black poultry at 0.25 h pd followed by a gradual decline in concentration and was below detection limit at 8 h pd. Plasma concentration of both ceftriaxone and tazobactam also did not show significant inter breed variation (between broiler, Rhode Island Red and Haringhata black breeds) at different time intervals. The plasma concentration of ceftriaxone and tazobactam also maintained an 8:1 ratio following single intramuscular administration @ 25 mg kg^{-1} and 3.125 mg kg^{-1} respectively in all three breeds of poultry.

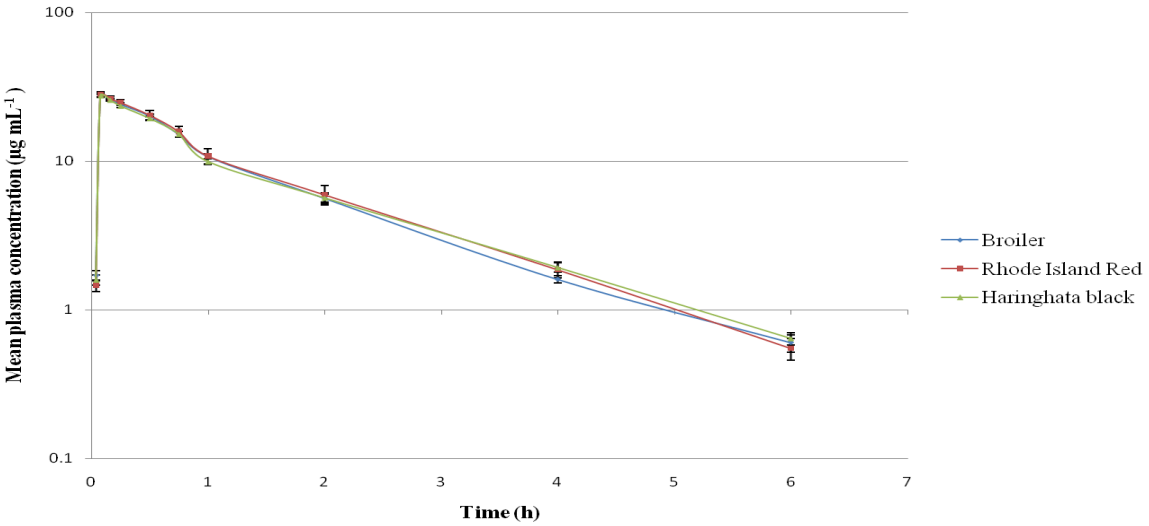

Figure 1: Semi-logarithmic plot of mean plasma concentration of ceftriaxone in broiler, Rhode Island Red and Haringhata black poultry following single intramuscular administration @ 25 mg kg^{-1}.

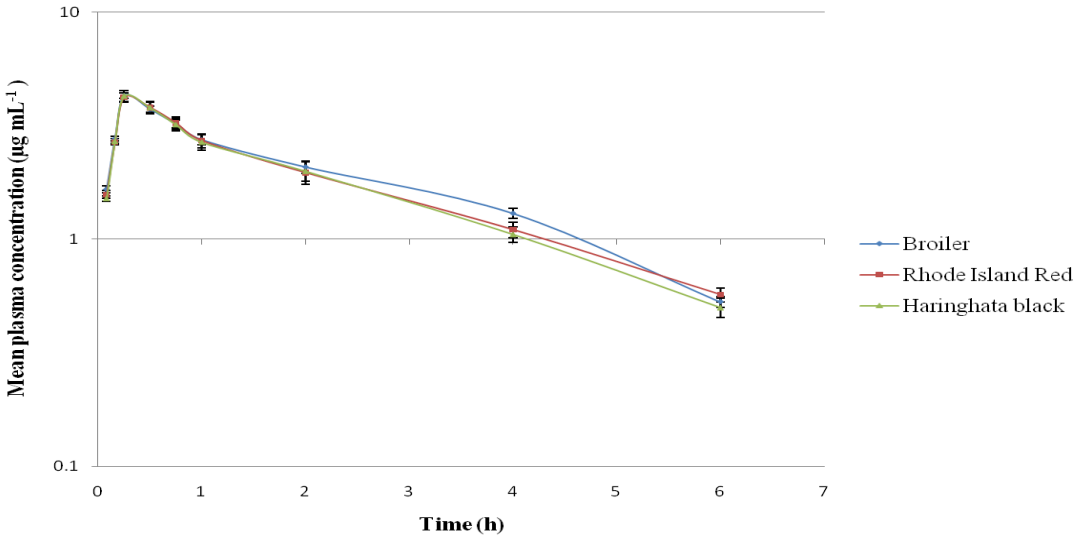

Figure 2: Semi-logarithmic plot of mean plasma concentration of tazobactam in broiler, Rhode Island Red and Haringhata black poultry following single intramuscular administration @ 25 mg kg^{-1}.

The pharmacokinetic parameters of ceftriaxone @ 25 mg kg^{-1} and tazobatam @ 3.125 mg kg^{-1} following intramuscular administration in broiler, Rhode Island Red and Haringhata black poultry were presented in table 1 and table 2 respectively. Both ceftriaxone and tazobactam followed "two compartment open model" in all breeds of poultry.

The absorption half life ($t_{½}$ K_a) values of ceftriaxone following single intramuscular administration was significantly smaller in broiler, Rhode Island Red and Haringhata black poultry (0.02. 0.01 and 0.02 h, respectively). Kumar el al. (2010) also reported a lower absorption half life of ceftriaxone in layer birds (0.18 h) following intramuscular administration @ 50 mg kg^{-1}.[13] Lower $t_{½}$ K_a values of both the studies indicated that ceftriaxone absorbed at a much faster rate in poultry following intramuscular administration and can quickly achieve therapeutic plasma concentration. The volume of distribution (Vd_{area}) of ceftraxone was found to be 1.04±0.04, 1.03±0.08 and 1.09±0.03 L kg^{-1} respectively in broiler, Rhode Island Red and Haringhata black poultry. The Vd_{area} of ceftriaxone was reported to be 3.18±0.39 L kg^{-1} in layer birds[13] and 0.53±0.05 L kg^{-1} in goats[14] following single intramuscular administration @ 50 mg kg^{-1} and 20 mg kg^{-1}, respectively. The elimination half life (t½ β) of ceftriaxone in broiler, Rhode Island Red and Haringhata black poultry was recorded to be 1.06±0.03, 1.05±0.03 and 1.11±0.02 h respectively. The elimination half life of ceftriaxone was reported to be 1.39±0.13 h in layer birds[13] and 1.9 h in calves[15] following single intramuscular administration. First order rate constant for transfer of drug from central compartment to peripheral compartment (K_{12}) as well from peripheral compartment to central compartment (K_{21}) was also significantly higher in Rhode Island Red

poultry compared to broilers and Haringhata black poultry.

Table 1: Pharmacokinetic parameters of ceftriaxone in broiler, Rhode Island Red and Haringhata black poultry following single intramuscular administration @ 25 mg kg^{-1} (n=6).

Kinetic Parameters	Broiler	Rhode Island Red	Haringhata black
C^0_P (µg mL^{-1})	49.34±1.52	50.95±3.63	47.11±0.95
A (µg mL^{-1})	24.74±0.76	25.55±1.81	23.60±0.48
B (µg mL^{-1})	24.59±0.76	25.41±1.82	23.51±0.47
K_a (h^{-1})	45.16±3.17	50.89±6.65	39.33±2.55
$t_{½}$ K_a (h)	0.02±0.00	0.01±0.00	0.02±0.00
β (h^{-1})	0.66±0.02	0.67±0.02	0.63±0.01
$t_{½}$ β (h)	1.06±0.03	1.05 ± 0.03	1.11±0.02
AUC (µg h mL^{-1})	37.93±1.01	39.00±3.35	38.22±0.85
Vd_{area} (L kg^{-1})	1.04±0.04	1.03±0.08	1.09±0.03
Cl_B (L kg^{-1} h^{-1})	11.40±0.35	11.44±1.01	11.39±0.23
MRT (h)	1.46±0.03	1.46±0.05	1.55±0.03
Vd_c (L kg^{-1})	0.51±0.02	0.50±0.03	0.53±0.01
Vd_{ss} (L kg^{-1})	1.05±0.03	1.03 ± 0.07	1.10±0.02
K_{12} (h^{-1})	21.67±1.56	24.53±3.34	18.78±1.29
K_{21} (h^{-1})	22.84±1.60	25.71±3.32	19.94±1.27
K_{el} (h^{-1})	1.30±0.03	1.32±0.04	1.23±0.02
f_c	0.51±0.00	0.50±0.00	0.51±0.00
T~P	0.98±0.00	0.98±0.00	0.97±0.00
C_{max}_calc (µg mL^{-1})	22.77±0.72	23.62±1.88	21.61±0.46
T_{max}_calc (h)	0.14±0.01	0.13±0.01	0.15±0.01

Tazobactam also showed a lower t½ Ka value of 0.09±0.01, 0.08±0.01 and 0.08±0.01 h respectively in broiler, Rhode Island Red and Haringhata black poultry similar to ceftriaxone following single intramuscular administration. The t½ β of tazobactam was recorded to be 2.05±0.07, 2.05±0.08 and 1.94±0.10 h respectively in broiler, Rhode Island Red and Haringhata black poultry. The clearance (Cl_B) was calculated to be 11.40±0.35, 11.44±1.01 and 11.39±0.23 L kg^{-1} h^{-1} respectively in broiler, Rhode Island Red and Haringhata black poultry following single intramuscular administration @ 3.125 mg kg$^{-1.}$

Table 2: Pharmacokinetic parameters of tazobactam in broiler, Rhode Island Red and Haringhata black birds following single intramuscular administration @ 3.125 mg kg^{-1} (n=6).

Kinetic Parameters	Broiler	Rhode Island Red	Haringhata black
C^0_P (µg mL^{-1})	8.55±0.40	8.36±0.55	8.53±0.65
A (µg mL^{-1})	4.26±0.19	4.18±0.27	4.27±0.32
B (µg mL^{-1})	4.29±0.21	4.18±0.27	4.26±0.33
K_a (h^{-1})	9.12±1.67	9.23±1.74	9.28±1.21
$t_{½}$ K_a (h)	0.09±0.01	0.08±0.01	0.08±0.01
β (h^{-1})	0.34±0.01	0.34±0.01	0.36±0.02
$t_{½}$ β (h)	2.05±0.07	2.05±0.08	1.94±0.10
AUC (µg h mL^{-1})	13.17±0.51	12.83±0.82	12.31±0.76
Vd_{area} (L kg^{-1})	0.76±0.04	0.79±0.05	0.77±0.06
Cl_B (L kg^{-1} h^{-1})	4.24 ± 0.14	4.46±0.25	4.62±0.29
MRT (h)	3.00±0.12	3.06±0.13	2.88±0.17
Vd_c (L kg^{-1})	2.96±0.15	3.06±0.20	3.01±0.22
Vd_{ss} (L kg^{-1})	6.48±0.22	6.65±0.36	6.55±0.40
K_{12} (h^{-1})	4.07±0.85	4.14±0.88	4.13±0.61
K_{21} (h^{-1})	4.74±0.82	4.78±0.86	4.82±0.61
K_{el} (h^{-1})	0.65±0.02	0.65±0.02	0.69±0.03
f_c	0.52±0.00	0.52±0.00	0.52±0.00
T~P	0.91±0.02	0.92±0.01	0.92±0.01
C_{max}_calc (µg mL^{-1})	3.56±0.10	3.48±0.18	3.54±0.20
T_{max}_calc (h)	0.42±0.04	0.42±0.03	0.40±0.03

Both ceftraxone and tazobactam showed favourable disposition kinetics in broiler, Rhode Island Red and Haringhata black poultry following single intramuscular administration @ 25 mg kg^{-1} and 3.125 mg kg^{-1} respectively. The values of different pharmacokinetic parameters of both ceftriaxone and tazobactam also did not vary significantly between the studied breeds of poultry and the plasma concentration of ceftriaxone and tazobactam maintained a ration 8:1. Ceftriaxone also maintained the reported minimum inhibitory concentration (MIC) of 0.12 µg mL^{-1} against inoculums of 10^5 and 10^6 c.f.u. mL^{-1} of TEM-1 containing *Escherichia coli*.[6] Therefore ceftriaxone-tazobactam combination (28.125 mg) at ratio of 8:1 containing ceftriaxone 25 mg and tazobactam 3.125 mg may effectively be used in poultry to treat ESBL producing bacterial infection and to prevent the spread of resistant bacteria through poultry and poultry meat products.

CONFLICT OF INTEREST: The authors declare no conflict of interest.

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