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Safety Evaluation of repeated oral administration of Gemifloxacin in Broiler Birds

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Abstract

Gemifloxacin is a fourth generation fluoroquinolone drug having broad-spectrum and good antibacterial activity at low plasma/tissue concentration. The present study was designed to investigate safety of gemifloxacin @ 10 mg/kg body weight after repeated oral administration at 24 hr interval for 5 days in 6 broiler birds of 5-6 week age. It was found safe based on non-significant alteration in haematological (Hb, PCV, TEC and TLC) and serum biochemical (AST, ALT, ACP, ALP, LDH, creatinine, total bilirubin and uric acid) parameters that were evaluated before and at 24 hourly interval for 5 days during treatment.

Key Words: Gemifloxacin, Broiler birds, Haematology, Serum Biochemistry

Introduction

Fluoroquinolones are gaining wide spread acceptance in veterinary medicine as they have broad spectrum activity against Gram-negative and Gram-positive bacteria, *Mycoplasma* spp., *Ricketsia* spp. as well as bacteria resistant to other antibiotics (Brown, 1996). Resistance of bacteria against fluoroquinolone is a great threat for future survival of the fluoroquinolone drugs as an antibacterial class in veterinary medicine (Sharma *et al.,* 1994). Gemifloxacin is a potent, novel broad spectrum fluoroquinolone antibacterial compound with enhanced affinity for bacterial topoisomerase IV and is developed for the treatment of respiratory and urinary tract infections (Hohl *et al.,* 1998). It has shown potent antibacterial activity against clinical isolates and reference strains both *in vitro* studies and experimental models of infection in animals (Berry *et al.,* 2000). Gemifloxacin is particularly active against Gram-positive organisms including penicillin, macrolide and quinolone-resistant *Streptococcus pneumonia* (Hardy *et al.,* 2000). It has also shown potent activity against other major pathogens involved in respiratory tract infections, including *Haemophilus influenza* and *Moraxella catarrhalis* and the atypical organisms, *Legionella pneumophila*, *Chlamydia spp.* and *Mycoplasma spp.* (Felmingham *et al.,* 1999). However, the data on safety of repeated oral administration of gemifloxacin in broiler birds are lacking. Therefore, the present study was planned to evaluate safety of gemifloxacin following multiple oral dose administration in broiler birds for effective use of this drug on a rational basis.

Materials and Methods

Experimental Animals: The study was conducted on 6 broiler birds of 5-6 weeks age weighing 1.5 to 2 kg during May-June when the ambient temperature was between 30-40°C. The birds were kept on Poultry Research Station of the College in Anand. The birds were kept under constant observation for at least 5 days before commencement of experiment. They were housed in clean cages and maintained on standard broiler ration as followed on the Station. The experimental protocol was approved by the Institutional Animal Ethics Committee of the College (IAEC/GVC/VPT/248/2016). Water was provided *ad libitum*. All necessary managemental procedures were adopted to keep the birds free from stress.

Drugs and Chemicals: Gemifloxacin tablets (Lupin Pharmaceuticals Limited, Mumbai) were purchased from local market. Standard assay kits used for serum biochemical analysis were purchased from Coral Clinical System, Goa, India.

Experimental Design: Safety of repeated oral administration of Gemifloxacin @ 10 mg/kg b. wt. once daily for 5 consecutive days was assessed by daily estimating haematology and serum biochemistry parameters.

Collection of Blood: Blood samples from all six birds were withdrawn from wing vein into sterile heparinized and non-heparinized test tubes at 0 day (before drug administration) and on 1st, 2nd, 3rd, 4th and 5th day for haematological and serum biochemical analysis. Blood samples (1 ml) collected in heparinized test tubes were utilized for haematological evaluation within 36 hrs and those collected in non-heparinized tubes (2 ml) were allowed to clot at room temperature. Serum was collected by centrifugation at 3000 rpm for 10 minutes and stored at –60°C for biochemical analysis.

Haemato-Biochemical Evaluation: Haematological parameters like haemoglobin, packed cell volume, total erythrocyte count and total leukocyte count were estimated with the help of auto-haematology analyzer (Mindray BC-2800 Vet). Serum biochemical parameters such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), acid phosphatase (ACP), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), creatinine, bilirubin (total) and uric acid were estimated using standard assay kits (Coral kit) with the help of auto-biochemistry analyzer (Photometer model 5010 VS^{+}, Germany).

Statistical Analysis: The data generated were compared by least square difference test using SPSS software (version 20), and are presented as Mean ± SE.

Results and Discussion

Haematological Parameters

The effect of multiple dose oral administration of gemifloxacin @ 10 mg/kg, daily once for five consecutive days on haematological parameters of broiler birds is shown in Table 1. The average values of haemoglobin, pack cell volume, total erythrocyte count and total leucocyte count observed for consecutive five days in treated birds did not differ significantly ($p<0.05$) from the corresponding values observed on day zero. Similar non-significant alteration in haematological parameters following gatifloxacin and levofloxacin administration @ 10 mg/kg dose of for 14 days in broiler (Devada *et al*., 2012 and Varia *et al.,* 2012) and in layer (Patel *et al.,* 2009 and Patel, 2010) birds has been reported earlier. Veerapandian *et al.* (2012) reported significant ($p<0.05$) elevation of heterophils and decrease in lymphocyte count on 1st and 3rd day post enrofloxacin treatment in broiler chicken at therapeutic dose of 10 mg/kg b.wt. through drinking water for five consecutive days, and opined that the reduction in the lymphocyte count at given therapeutic dose may have influence on the immune response of the birds.

Serum Biochemical Parameters

The effect of multiple dose oral administration of gemifloxacin (10 mg/kg, daily once for five

Table 1: Effect of multiple dose oral administration of gemifloxacin (10 mg/kg, daily once) on hematological parameters (Mean ± SE) of broiler birds (n=6)

Days	Hematological parameters			
	TEC (10^6/µl)	Hb (g/dl)	PCV (%)	TLC (10^3/µl)
0	3.22±0.04	10.45±0.28	29.85±0.58	66.11±0.59
1	3.11±0.15	10.83±0.19	29.47±0.95	64.64±0.45
2	3.26±0.09	10.88±0.43	30.53±0.89	67.42±0.49
3	3.54±0.14	10.92±0.31	30.38±0.81	67.29±0.42
4	3.43±0.10	11.47±0.34	31.55±1.70	65.57±0.86
5	3.44±0.13	11.75±0.36	28.48±0.40	66.67±0.67

Mean values did not differ significantly between days ($p>0.05$) for any of the parameters.

Table 2: Effect of multiple dose oral administration of gemifloxacin (10 mg/kg, daily once) on serum biochemical parameters (Mean ± SE) of broiler birds (n=6)

Days	Serum biochemical and enzymatic profile							
	ALT (IU)	AST (IU)	ACP (IU/L)	ALP (IU/L)	LDH (IU)	Creatinine (mg/dl)	Bilirubin (mg/dl)	Uric Acid (mg/dl)
0	25.93±1.16	228.62±4.62	5.65±0.19	123.86±1.28	631.47±40.16	0.28±0.01	0.17±0.01	8.03±0.15
1	27.15±1.11	226.31±3.36	5.59±0.12	124.16±1.48	636.61±20.63	0.29±0.01	0.16±0.01	8.16±0.12
2	27.95±1.22	229.33±2.71	5.16±0.14	123.08±1.51	736.85±63.64	0.28±0.01	0.18±0.01	8.00±0.12
3	26.68±0.59	233.11±2.51	5.65±0.16	123.80±1.39	688.40±51.70	0.29±0.01	0.16±0.01	8.22±0.14
4	26.64±1.11	225.34±2.57	5.54±0.21	122.82±0.87	688.03±51.77	0.27±0.01	0.16±0.01	8.03±0.13
5	28.49±1.43	225.37±4.01	5.33±0.13	125.13±0.94	737.91±62.99	0.28±0.01	0.18±0.01	8.17±0.18

Mean values did not differ significantly between days ($p>0.05$) for any of the parameters.

consecutive days) on liver and kidney functions evaluated through serum biochemical parameters of broiler birds is presented in Table 2. The mean values of serum alanine aminotransferase, aspartate aminotransferase, acid phosphatase, alkaline phosphatase, lactate dehydrogenase, creatinine, total bilirubin and uric acid estimated on different days of treatment did not differ significantly ($p<0.05$) from the serum values observed on day zero. Patel (2010) and Devada *et al.* (2012) found non-significant alteration in blood biochemical parameters following repeated administration of gatifloxacin at 10 mg/kg dose for 14 days in layer and broiler birds, respectively. Patel *et al.* (2009) and Varia *et al.* (2012) also found similar non-significant alteration in blood biochemical parameters following repeated administration of levofloxacin at 10 mg/kg dose for 14 days in layer and broiler birds, respectively. Gajjar *et al.* (2000) evaluated the single and multiple-dose safety and tolerability of gatifloxacin administered as daily 1-hour intravenous infusions for 14 days in healthy adult men. They observed that parenteral gatifloxacin doses were well tolerated by healthy volunteers with mild and transient intravenous site reaction and a mild transient decrease in serum glucose was associated with the end of the 1-hr infusion of gatifloxacin. Similarly, Veerapandian *et al.* (2013) did not find significant change ($p>0.05$) in serum total protein, albumin, lactate dehydrogenase, alkaline phosphatase, creatine kinase, lipase, triglyceride and urea levels

at 24 and 48 h intervals during the dosing in broiler chickens administered enrofloxacin @ 10 mg/kg body weight via drinking water for five successive days. However, a significant increase ($p<0.05$) in gamma glutamyltransferase, uric acid and creatinine levels were observed after the 1st and 4th dose of the enrofloxacin and on day 1 post treatment. During the withdrawal period, the elevated levels declined gradually and showed the trend towards control values by day 3-9 post-treatment.

Conclusions

It is apparent from the results of non-significant haemato-biochemical alterations that oral administration of gemifloxacin at the dose rate of 10 mg/kg body weight repeated at 24 hr interval for five days in broiler birds is safe.

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Conflict of Interest: All authors declare no conflict of interest.

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