

*Full Length Research Paper*

# Anxiogenic potential of prulifloxacin in experimental animal model

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**Prulifloxacin, the prodrug of ulifloxacin, is a broad spectrum oral fluoroquinolones antibacterial agent. Fluoroquinolones have been used for the treatment of bacterial infection for many years. Although they were considered as relatively safe drugs, various adverse effects have recently been reported along with increase in the usage of new generation fluoroquinolones. In the present study, prulifloxacin 200 and 400 mg/kg were screened on anxiety parameter in mice. Our result suggested that prulifloxacin (200 and 400 mg/kg) exerted anxiety-like effect in the elevated plus maze, hole board apparatus and light/dark exploration test in mice.**

**Key words:** Prulifloxacin, elevated plus maze, hole board apparatus, light/dark exploration test.

## INTRODUCTION

Fluoroquinolones are one of the most widely prescribed classes of antimicrobial. Although generally tolerated, central nervous system effects are the second most common type (after gastrointestinal) of adverse drug reactions (ADR's) reported with fluoroquinolones. These include mild reactions including headache, confusion, dizziness, tiredness, insomnia, anxiety or more severe psychotic reactions, agitation, hallucinations, nightmare, restlessness, depression and seizures reported clinically. The severe reactions are rare, occurring in less than 0.5% (Cross, 2001). A variety of neurobehavioral adverse effects, other than seizures have been reported with fluoroquinolones. For example in a single case report, ciprofloxacin was associated with psychosis in women with no psychiatric history (Bharal et al., 2006). Similarly, levofloxacin produced anxiety like effects in rodent experimental models (Erden et al., 2001).

Prulifloxacin is one of the newer generations of fluoroquinolones. The neurobehavioral effects of fluoroquinolones have been reported experimentally as well as clinically for drugs like ciprofloxacin, norfloxacin,

pefloxacin, ofloxacin etc. Sparfloxacin have been reported for insomnia, sleep disorders and convulsions (Erden et al., 2001). Prulifloxacin is a new thiazeto-quinolones antibacterial agent prodrug of the quinolone carboxylic acid ulifloxacin characterized by a potent and broad-spectrum antibacterial activity. It has been reported to produce nausea, dizziness, insomnia and agitation (Matera, 2006). Such anxiety effects have been reported with ciprofloxacin, norfloxacin, gatifloxacin, sparfloxacin and levofloxacin in experimental animals. The anxiogenic effect could well be related to inhibition of GABA<sub>A</sub> receptor complex (Johnstone et al., 2004). Quinolones have an inhibitory effect on the receptor binding of GABA<sub>A</sub>, and may thus exert an inhibitory CNS stimulant action (Akahane et al., 1994). The adenosine or GABA<sub>A</sub> receptor has therefore been proposed as a possible target for quinolones, particularly with older agents like norfloxacin and ciprofloxacin, and less so with pefloxacin (Dodd et al., 1988). N-methyl-D-aspartate (NMDA) receptors present in the hippocampus may also be responsible for the anxiogenic property exhibited as side effects of fluoroquinolones (Sen et al., 2007). However, experimental evidence is still needed to study its neurobehavioral effects. In the present study, we investigated the neurobehavioral effects of prulifloxacin on experimental models of anxiety.

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**Table 1.** Effect of short term (7 days) administration of prulifloxacin on elevated plus maze.

Group no.	Dose and drug	Number of entries		Time spent by the animal (s)	
		Open arm	Closed arm	Open arm	Closed arm
I	Control	4 ± 2.08	8.6 ± 2.6	24.6 ± 15.16	275 ± 15.17
II	Prulifloxacin (200 mg/kg)	4 ± 0.57	7.3 ± 0.33	23.6 ± 9.3*	276 ± 9.4
III	Prulifloxacin (400 mg/kg)	2.6 ± 1.76	5 ± 2.3	24 ± 7.2*	275 ± 7.2

Values are expressed as mean ± SD. \*Indicates statistical significance in comparison to the control treatment; \* denote p < 0.01 respectively by student t pair test. n = 5.

**Table 2.** Effect of short term (7 days) administration of prulifloxacin on hole board apparatus.

Group no.	Treatment	Dose	Number of head poking during 5 min
I	Control	Saline	102 ± 7.79
II	Prulifloxacin	200 mg/kg	34 ± 2.3*
III	Prulifloxacin	400 mg/kg	17.6 ± 1.2*

Values are expressed as mean ± SD. \* Indicates statistical significance in comparison to the control treatment; \*denote p < 0.005 by student t pair test. n = 5.

## MATERIALS AND METHODS

Both sexes of albino mice were used for this study. Animals were housed in groups of five in standard polypropylene laboratory cages at an ambient temperature of 25 ± 2°C and 45 to 55% relative humidity with reversed 12:12 h light/dark cycle. They had free access to rodent chow and tap water *ad libitum*. The animal studies were carried out after getting approval from the institution of animal ethical committee.

Prulifloxacin were freshly prepared dissolved in distilled water and administered intraperitoneally in the morning for seven consecutive days. A dose of 200 and 400 mg/kg was chosen for the present study. The control animals were given the same volume of distilled water. Separate groups of mice were used for each behavioral test. Elevated plus maze, hole board apparatus, light/dark exploration test were employed in this test. Experiments were performed on the seventh day, 45 min after the drug administration.

### Elevated plus maze

The elevated plus maze consisted of two opposite arms (50 cm × 10 cm) crossed with two opposite enclosed arms of the same dimension with 40 cm high walls. The arms were connected with a central square (10 cm × 10 cm) to give the apparatus a plus sign appearance. The maze was kept elevated 50 cm above the floor in a dimly-lit room. The mice were individually placed on the central square of the plus maze facing on enclosed arm. The time spent and numbers of entries made by the mice, during the next 5 min, on open and enclosed arms were recorded. An arm entry was defined when all the four limbs were on the arm (Sen, 2007).

### Hole board test

The hole board apparatus consisted of a wooden box (40 × 40 × 25 cm<sup>3</sup>) with 16 holes (each of diameter 3 cm) evenly distributed on the base of box. The apparatus was elevated to the height of 25 cm. Mice were treated with prulifloxacin 200 and 400 mg/kg before they were placed in the apparatus. The number of head pokes and

the time of head dipping during a 5 min period were recorded (Barua et al., 2009).

### Light/dark exploration test

The apparatus consisted of a dark compartment (13 × 22 × 26 cm<sup>3</sup>) connected by a 5 × 5 cm<sup>2</sup> window to a bright compartment (illuminated, 600 lux, 23 × 22 × 26 cm<sup>3</sup>). Mice were placed in the dark compartment and activity was measured for 5 min. The percent time spent in the bright compartment and number of entries into the bright compartment were used as an index of the anxiety state of mice (Suzuki et al., 2007).

## RESULTS

The effects of prulifloxacin treatments on the behavior of mice in the elevated plus maze, hole board apparatus and light/dark exploration test shown in Tables 1, 2 and 3, and Figure 1, 2 and 3. In the elevated plus maze, prulifloxacin treated mice spent significantly more time and made more number of entries to the enclosed arms, and decreasing the time spent in open arms. The results of the ratio between open arm and enclosed arm time and entries also indicated that both doses of prulifloxacin caused significant anxiogenic behavior in mice. In hole board apparatus, both doses 200 and 400 mg/kg showed anxiogenic response by significantly reduced the number of head poking. Reduction of number of entries in the bright side and increase of time spent by the animal in dark side were observed in the light/dark exploration test.

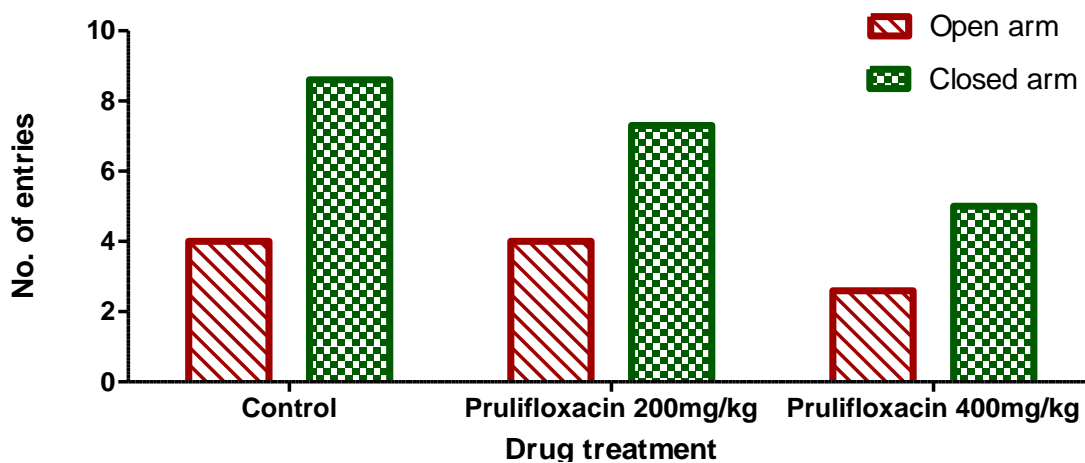
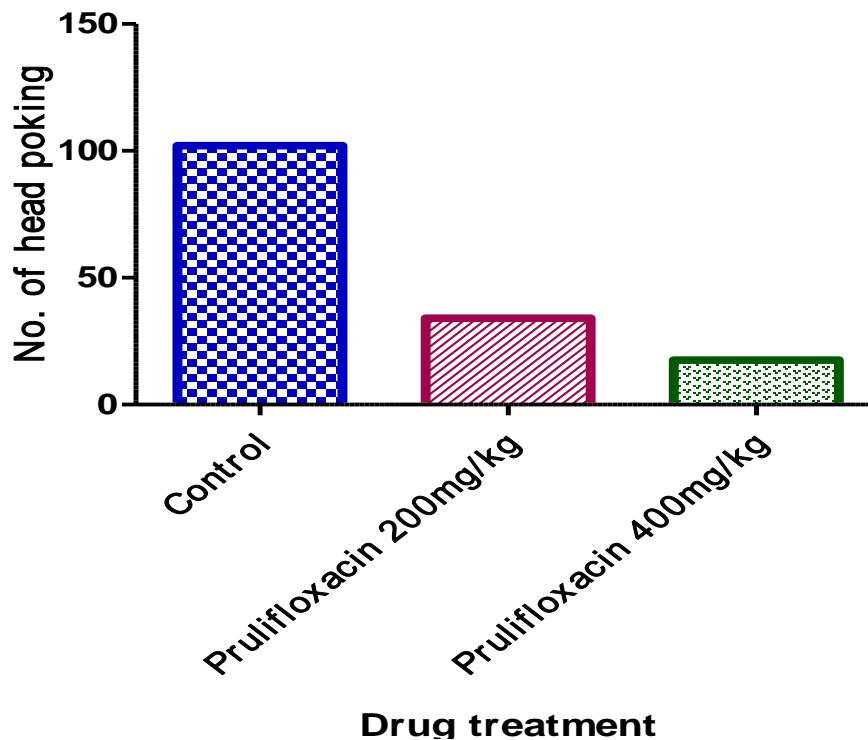
## DISCUSSION

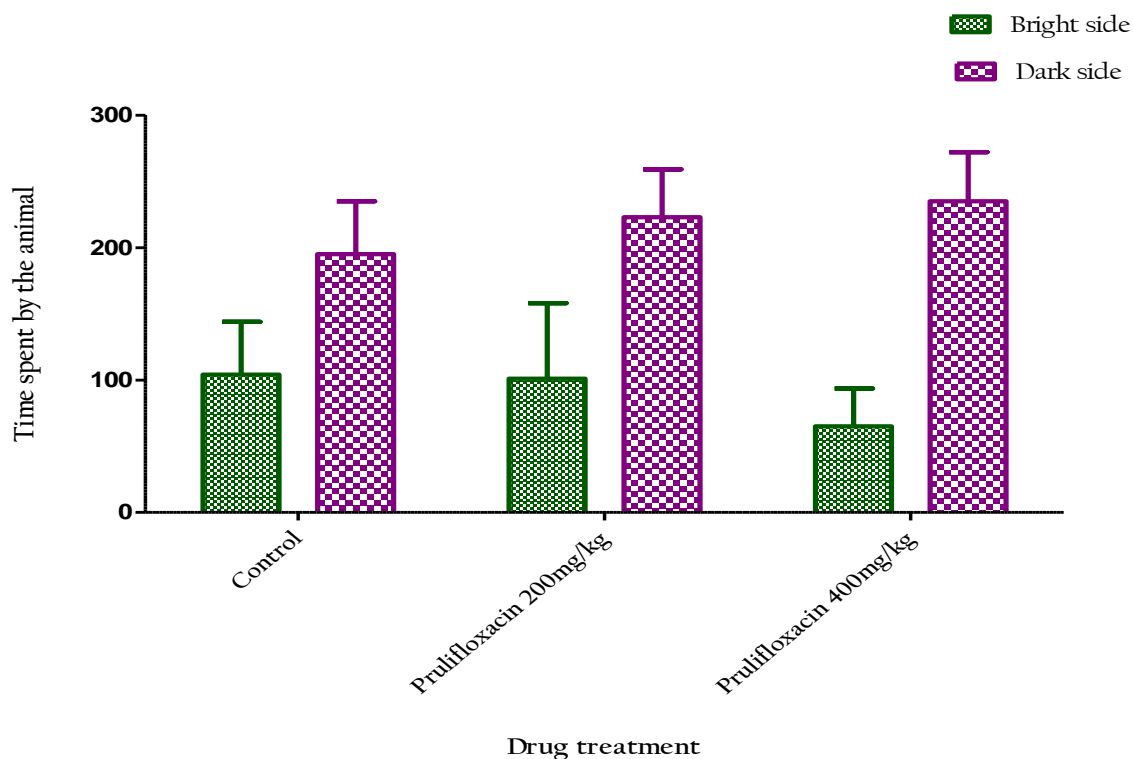
Fluoroquinolones are widely prescribed antimicrobial

**Table 3.** Effect of short term (7 days) administration of Prulifloxacin on light/dark exploration test.

Group no.	Treatment and dose	Time spent (s)		No. of entries in bright side
		Bright side	Dark side	
I	Control	104 ± 40	195 ± 40	6.25 ± 0.91
II	Prulifloxacin (200 mg/kg)	101 ± 57	223 ± 36	2.25 ± 0.47*
III	Prulifloxacin (400 mg/kg)	65 ± 28.6	235 ± 37	2.3 ± 1.4**

Values are expressed as mean ± SD. \* Indicates statistical significance in comparison to the control treatment; \*denote  $p < 0.005$  and \*\* denote  $p < 0.025$  by student t pair test.  $n = 5$ .

**Figure 1.** Effect of seven days administration of prulifloxacin on elevated plus maze.**Figure 2.** Effect of seven days administration of prulifloxacin on hole board apparatus.



**Figure 3.** Effect of seven days administration of prulifloxacin on light/dark exploration test.

agents although convenient to administer, and have been reported to have some adverse drug reactions on the CNS during their clinical usage. The present study was conducted to investigate the neurobehavioral effects of prulifloxacin in mice. In 7 days administration study, the results indicate that prulifloxacin at 200 and 400mg/kg, i.p dose showed anxiogenic effects as indicated by decreased number of entries and time spent in closed arms. In hole board apparatus, they showed reduced the number of poking. In light/dark exploration test, they reduced the number of entries in bright side. Such anxiety effects have been reported with ciprofloxacin, norfloxacin, gatifloxacin, sparfloxacin and levofloxacin in experimental animals. More recently, however, an anxiolytic effect has been reported by modifying norfloxacin. The anxiogenic effect could well be related to inhibition of GABA<sub>A</sub> receptor complex (Johnstone et al., 2004).

The role of gamma-aminobutyric acid (GABA) in anxiety is well documented (Sen et al., 2007). Some studies indicate that fluoroquinolones function as GABA receptor antagonists (Unsel et al., 1990) and the epileptogenic action of quinolones has been proposed to be related to the GABA-like structure of ring substitutes. The central nervous system (CNS) effects of pefloxacin in clinical settings have been explained by some reported biochemical studies. Quinolones have an inhibitory effect on the receptor binding of GABA<sub>A</sub>, and may thus exert an

inhibitory CNS stimulant action (Akahane et al., 1994). The adenosine or GABA<sub>A</sub> receptor has therefore been proposed as a possible target for quinolones, particularly with older agents like norfloxacin and ciprofloxacin, and less so with pefloxacin (Dodd et al., 1988). The excitatory potentials of fluoroquinolones have been reported to be increased in a dose dependent manner in the electrophysiological studies of the field potentials in the CA 1 region of the rat hippocampus slice (Schmuck et al., 1998). N-methyl-D-aspartate (NMDA) receptors present in the hippocampus may also be responsible for the anxiogenic property exhibited as side effects of fluoroquinolones (Sen et al., 2007).

## Conclusion

The present study indicates that prulifloxacin produces anxiogenic response at the dose of 200 and 400 mg/kg on experimental animal model.

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