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ANXIOGENIC EFFECT OF MOXIFLOXACIN IN WISTAR RATS

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ABSTRACT

Objective: The study was carried out toevaluate whether moxifloxacin can cause anxiety in rats.**Materials and Methods:** Elevated plus maze and open field test were used to assess the anxiogenic activity of moxifloxacin. Four groups of rats were treated orally with distilled water (10 ml/kg), levofloxacin (40 mg/kg) andmoxifloxacin (36 mg/kg and 72 mg/kg), respectively. The time spent, number of entries, rears in the arms of the elevated plus maze and central and peripheral areas in the open fieldwere observed.

Results: Moxifloxacin (both doses) significantly increased ($P<0.05$) the time spent in the closed arms of elevated plus maze and significantly decreased ($P<0.05$) the time spent in the open arms of the elevated maze and central area in the open field as compared to control. The number of entries in the central area was significantly decreased ($P<0.05$) in moxifloxacin and levofloxacin treated rats. The number of rearings was significantly decreased ($P<0.05$) in both arms of the elevated plus maze and peripheral areas of open field in moxifloxacin and levofloxacin treated groups.

Conclusion: Moxifloxacin produced anxiogenic activity in wistarrats.

KEY WORDS: anxiety, moxifloxacin, elevated plus maze, open field.

INTRODUCTION

Fluoroquinolones are antimicrobial agents which are primarily active against gram negative aerobic bacteria.The newer fluoroquinolones, levofloxacin and moxifloxacin, have high activity against gram positive bacteria(Petri WA, 2006). Levofloxacin and moxifloxacin are also effective against *Mycobacterium tuberculosis* (Chambers HF and Deck DH, 2009a).These drugs are generally well tolerated. The common adverse effects are related to the gastrointestinal tract-they include nausea, vomiting and diarrhea. Less frequently,CNS side effects like dizziness,headache and insomnia have been reported(Chambers HF and Deck DH, 2009b).Ciprofloxacin,norfloxacin and levofloxacin have been found to have anxiogenic effect inelevated plus maze in rats (Sen et al., 2007; Erden et al.,2001).Hence,it was decided to evaluate the effect of moxifloxacin on the behavior of rats in the elevated plus maze and open field.

MATERIALS ANDMETHODS

Drugs

Moxifloxacin tablet (Cipla Pharmaceuticals Ltd.) and levofloxacin tablet (Piramal Healthcare)werepurchasedfrom thepharmacyofKasturba Hospital, Manipal.

Animals

Adultmale,wistaralbinoratsweighing150-200gwereusedinthestudy.Theratsweremaintainedunder standardconditionsinCentralAnimalHouse,ManipalUniversity,ManipalapprovedbytheCommitteeforthePurposeofControlandSupervisionofExperimentsonAnimals(CPCSEA).Theratswerekeptinpolypropylenecages(U.N.Shahmanufacturers,Mumbai)andmaintainedonstandardpelletdiet(AmrutLabAnimalFeed,PranavAgroIndustriesLtd,Sangli,Maharashtra)andwateradlibitum.Theratsweremaintainedona12:12hourlight-darkcycle. Experimentswereperformedduringthedarkcycle.

Studydesign

Thestudywasundertakenafterobtainingpermissionfromthe InstitutionalAnimalEthicsCommittee, Manipal. Twenty four rats were used in this study. They were divided into four groups of six animalseach.

The treatment schedule was as follows –

Group 1- control, received distilled water in a dose of 10 ml/kg.

Group 2–received levofloxacin in a dose of 40mg/kg.

Groups 3 and4- received moxifloxacin in doses of 36mg/kg and 72mg/kg,respectively.

The drugs were givenonce daily, orally, for ten days. Levofloxacin was administered in a dose based on an earlier study(Erden et al.,2001).The doses of moxifloxacin were calculated based on the human dose (Ghosh,2005).On the 10^{th} day,the test to assess anxiety in rats was carried out 45 minutes after the last dose of the drugs. Two models were used in this study– elevated plus maze (EPM) and open field test (OFT).The apparatus in each model was wiped with 10% ethanol after trial witheach rat to eliminate possible bias due to odor of previous animal.

Elevatedplusmaze (EPM)

The Elevated plus maze is a model used to assess anxiety(Pellow S, et al.,1985). The apparatus has two open arms (50×10 cm) and two closed arms (50×10×40 cm), around a central square (10×10 cm), such that arms of the same type are opposite to each other.The maze is 50 cm above the ground. All the rats received drugs for ten days. On the 10^{th} day, 45 minutes after drug administration, each rat was placed in the central square of the maze facing one of the closed arms **(**Rodgers RJ and Dalvi A, 1997). The time spent, the number of entries and rears in each type of arm was recorded for 5 min (Walf AA and Frye CA,2007). The presence of all four paws in an arm was considered as an entry.

Openfieldtest (OFT)

In this test, anxiety was assessed by studying the exploratory pattern of the rat. The apparatus consists of a square arena 96 x 96 cm^2 with 60 cm high walls. The floor is divided into 25 squares. The central area has nine squares and peripheral area has sixteen squares along the walls. A 40W bulb illuminated the open field from a height of about 100 cm.The experimental room was sound attenuated, dark room. Four groups of rats were administered drugs for ten days. On the 10^{th} day, 45 minutes after drug administration, the rat was placed in a centre of the open field(Fernandez F, 2002).The time spent, number of lines crossed, entries and rearing in the central and peripheral areas was observed during a 5 minute exposure period. The presence of all four paws in an area was considered as an entry.

Statisticalanalysis

Allvaluesareexpressedasmean±SEM.Datawasanalyzedusingone-wayANOVA.Post-hoc comparisons were performedby applying Bonferronitest.$P<0.05$ wasconsidered statisticallysignificant.Allstatistical analyseswerecarriedout byusingSPSSfor Windows(SPSS17.0).

RESULTS

Elevated plus maze

In the elevated plus maze model, the time spent by moxifloxacintreated rats (36mg/kg and 72mg/kg) and levofloxacin in the open arm was significantly($P< 0.05$) decreased (63.33±9.48s, 59.00±2.82s, 70.50±9.81s, respectively)as compared to control (130.50±21.07s).The time spent in the closed arm by moxifloxacinand levofloxacin treated rats was significantly($P< 0.05$) increased as compared to control(Table 1).The number of rearings in both the arms was significantly($P< 0.05$) decreased in moxifloxacin (both doses) and levofloxacin treated rats as compared to control (Table 1). There was no significant difference between the effects of moxifloxacin and levofloxacin.

Table 1: Effect of moxifloxacin on the behavior of rats in elevated plus maze

Group/drug	Number of entries		Time spent in seconds(s)		Number of rears	
	Open arm	Closed arm	Open arm	Closed arm	Open arm	Closed arm
1/Distilled water (10ml/kg)	4.17±0.79	4.17±0.91	130.50±21.07	170.83±20.72	10.17±1.25	9.00±0.68
2/Levofloxacin (40 mg/kg)	2.33±0.61	5.00±1.86	70.50±9.81*	235.50±12.38*	1.51±0.50*	4.33±0.49*
3/Moxifloxacin(36mg/kg)	2.83±0.40	4.17±0.40	63.33±9.48*	236.17±9.02*	1.67±0.84*	3.00±0.52 *
4/Moxifloxacin (72 mg/kg)	3.50±0.43	3.33±0.42	59.00±2.82*	253.33±2.88*	0.83±0.17*	3.50±0.67*

Values are expressed as mean ±SEM, n = 6 in each group. *$P<0.05$ as compared to control. (ANOVA followed by Bonferroni's test)

Open field test

In the open field test, rats treated with moxifloxacin (36mg/kg and 72mg/kg) showed a significant ($P<0.05$) decrease in the number of entries in central area (2.67±0.12,2.33±0.42, respectively) as compared to control (9.67±0.80). The number of rearings in the periphery was significantly ($P<0.05$) decreased in levofloxacin and moxifloxacin treated groups with respect to control (Table 2). The time spent in the central area by moxifloxacin and levofloxacin treated rats was significantly ($P<0.05$) decreased as compared to control (Table 2).

Table 2: Effect of moxifloxacin on the behavior of rats in the open field model

Group	Number of lines crossed		Number of entries		Time spent in seconds (s)		Number of rears	
	centre	periphery	centre	periphery	centre	periphery		
1	16.00±2.79	58.16±3.19	9.67±0.80		56.67±12.87	243.33±12.87	2.81±1.22	12.00 ±0.68
2	12.33±2.04	45.70±1.33	5.50 ±2.83[a,b]		35.83±8.31[a]	244.32±8.36	1.93 ±0.31	8.17 ±0.60[a]
3	15.50± 1.91	44.50±2.17	2.67±0.12[a]		27.33±7.75[a]	271.01±7.92	1.56±0.16	7.33±0.56[a]
4	8.83 ±1.07	35.00±4.61	2.33±0.42[a]		26.83±5.90[a]	272.50±6.05	1.01±0.16	5.50±1.23[a]

Values are expressed as mean ± SEM, n = 6 in each group.
[a]P< 0.05 as compared to control ;
[b]P< 0.05 as compared to moxifloxacin 72mg/kg;
(ANOVA followed by Bonferroni's test)
Group 1- distilled water 10ml/kg; 2-levofloxacin 40mg/kg; 3-moxifloxacin 36mg/kg;
4 –moxifloxacin 72mg/kg.

DISCUSSION

The elevated plus maze is commonly used to assess anxiety related behavior.In the elevated plus maze, avoidance of the open arms, an increase in the time spent in the closed arms and a decrease in rearings indicates anxiety(Pellow S, et al.,1985; Fernandes C and File SE,1996). In our study, a decrease in time spent in open arms, increase in time spent in closed arms and a decrease in rearings in moxifloxacin treated rats indicates its anxiogenic effect.

In the open field test, the exploratory behavior of the animal is studied. There is a tendency for the animal to be close to the periphery of the apparatus (Bhattacharya SK and Satyan KS, 1997). In the open field test, animals show anxiety by a decrease in the number of entries and time spent in the centre. A decrease in the number of rearings also indicates anxiety. All these findings were present in the moxifloxacin treated rats in our study which shows its anxiogenic effect.

Various mechanisms have been proposed for CNS related adverse effects of fluoroquinolones. The inhibitory neurotransmitter GABA is known to play a role in anxiety. Ciprofloxacin and norfloxacin exert their anxiogenic effect probably by inhibiting the binding of GABA to its receptors (Sen et al., 2007). Studies have shown that the action on GABA receptor was less with pefloxacin and levofloxacin (Imanishi et al., 1995). Our study demonstrated anxiogenic activity of moxifloxacin in rats. Further studies are required to elucidate the mechanism involved in its anxiogenic effect.

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