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A COMPARATIVE STUDY OF ANXIOGENIC EFFECTS OF FLUOROQUINOLONES IN RATS

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Abstract : The present study compares the anxiogenic effects of three fluoroquinolones namely ciprofloxacin, ofloxacin and pefloxacin in rats using elevated plus–maze. The rats were treated with 12.5 mg/kg and 25 mg/kg of ciprofloxacin, ofloxacin or pefloxacin and then tested in elevated plus–maze half an hour later, for a period of 5 min. All the three fluoroquinolones decreased the time spent in open arm considerably. This decrease was statistically significant only with the higher doses of ciprofloxacin and ofloxacin ($P<0.05$). Mean time spent in closed arm was increased by all the test drugs in both the doses. Increase was statistically significant with both the doses of ofloxacin ($P<0.05$). Mean time spent in closed arm was increased by all the test drugs in both the doses. Increase was statistically significant with both the doses of ofloxacin ($P<0.05$, $P<0.01$ respectively) and higher doses of ciprofloxacin and pefloxacin ($P<0.01$, $P<0.05$ respectively). The number of entries in open arm and closed arm were decreased by both the doses of the three fluoroquinolones used in the study. The reduction in total number of arm entries by ciprofloxacin, ofloxacin and pefloxacin in both the doses was highly significant. The results suggest definite anxiogenic potential of fluoroquinolones.

Key words : anxiogenic ciprofloxacin ofloxacin pefloxacin elevated plus-maze

INTRODUCTION

The fluorinated quinolones especially ciprofloxacin, ofloxacin and pefloxacin are extensively used antimicrobials and are generally well tolerated with low frequency of serious adverse events (1). The overall incidence of adverse reactions in humans is reported to be 4–8%, the involvement of CNS being 0.7–2.2% (2). The quinolones can even cause severe CNS effects even after short term use (3). The CNS effects in humans include a variety of nonspecific reactions e.g. anxiety, depression, insomnia, dizziness, confusion and seizures (4, 5) and decreased locomotor activity and rotarod performance along-with minimal effects on general behavior in animals (6).

In the present study ciprofloxacin, ofloxacin and pefloxacin were tested for their anxiogenic potential in rats by elevated plus-maze. The doses of quinolones used, are derived from the clinically

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employed therapeutic doses. Drugs were administered intraperitoneally to minimise the variations in bioavailability.

METHODS

Animals

The study was carried out in albino rats (either sex) weighing 120–200 g. Rats were quarantined for at least 7 days before use, housed in groups of 6 animals in polypropylene cages and maintained on standard pellet diet (Hindustan Lever Ltd., Bombay) and water *ad libitum*. They were subjected to experimentation between 0900 hr-1600 hr in noise free atmosphere with ambient temperature 23–30°C.

Treatment

Ciprofloxacin, ofloxacin and pefloxacin were dissolved in normal saline. Each drug was used in two doses 12.5 mg/kg and 25 mg/kg intraperitoneally. Animals were randomly allocated to seven groups, each group containing ten animals. Animals were tested in elevated plus-maze, 30 min after drug administration. Control experiments were performed with the vehicle. All animals were conditioned to elevated plus-maze before being subjected to experimentation.

Apparatus

The elevated plus-maze consisted of two open arms (50×10 cms) and two enclosed arms (50 × 10 × 40 cms) arranged such that the arms of the same type are opposite to each other. The maze was fixed at a height of 50 cms above its base.

Procedure

Rats were placed individually on the central 'neutral' square between the four arms of plus-maze, half an hour after test drug. Entry into an arm was noted only when all four paws had crossed out of the central square into an arm area. During a 5 min test period the following measures were recorded: total number of entries; the number of entries into, and the total time spent in (a) open arms (OA) and (b) closed arms (CA) (7).

Statistics

Posthoc comparisons between the individual treatment groups and the control group were performed using Student's unpaired 't' test. Significance was defined as $P<0.05$.

RESULTS

Results are depicted in Table I. The number of entries in OA and CA were decreased significantly by both the doses of the three fluoroquinolones used. All the three fluoroquinolones in the two doses used, decreased the time spent in OA, though the decrease was statistically significant only with higher doses of ciprofloxacin and ofloxacin ($P<0.05$). Mean time spent in CA was increased by all the test drugs in both the doses. Increase was statistically significant with both the doses of ofloxacin ($P<0.05$, $P<0.01$ respectively), while only higher dose of ciprofloxacin and pefloxacin showed statistically significant increase ($P<0.01$, $P<0.05$ respectively).

TABLE I : Anxiety status of rats on elevated plus-maze.

Group	*Drug*	*Dose;route mg/kg; I.P*	*Total No. of arm entries*	*No. of entries in O.A.*	*No. of entries in C.A.*	*Time spent in O.A (in sec)*	*Time spent in C.A (in sec)*
I	Vehicle	0.25cc/100g	11 ± 0.4	4±0.3	7 ±0.6	42 ± 9.5	200 ± 15.4
II	Ciprofloxacin	12.5	7 ± 0.2***	2±0.2***	5 ±0.2*	22 ± 8.4	242 ± 17.2
III	Ciprofloxacin	25	5 ± 0.4***	1±0.1***	4 ±0.6**	17 ± 5.8*	263 ± 16.4**
IV	Ofloxacin	12.5	6 ± 0.6***	2±0.4***	4 ±0.4**	20 ± 7.9	259 ± 18.2*
V	Ofloxacin	25	6 ± 0.3***	1±0.5***	5 ±0.4*	14 ± 10.0*	275 ± 19.5**
VI	Pefloxacin	12.5	8 ± 0.2***	2±0.5***	6 ±0.2	30 ± 8.2	228 ± 10.5
VII	Pefloxacin	25	7 ± 0.4***	2±0.4***	5 ±0.5*	24 ± 6.7	249 ± 11.6*

Values are expressed as Mean ± SEM
*P<0.05; **P<0.01; ***P<0.001
Significantly different from control group (Group 1)
OA - Open Arm; CA-Closed arm

DISCUSSION

Since the discovery of beta carboline compounds which act at benzodiazepine receptors to induce anxiety in animals and in man, considerable interest has been centered around the investigation of anxiogenic drug effects (7). Insomnia, anxiety and restlessness are commonly reported adverse effects of fluoroquinolone antimicrobial agents. The present study was undertaken to compare anxiogenic potential of three fluoroquinolones e.g. ciprofloxacin, ofloxacin and pefloxacin in rats. In the this study, all the three fluoroquinolones in the two doses employed, decreased the total number of entries, decreased the open arm (OA), and closed arm (CA) entries, decreased the time spent in OA and increased the time spent in CA.

It was suggested that lipophilic character of quinolones may correlate with CNS reactions. However, the incidence of CNS reactions to pefloxacin, the most lipophilic of the three quinolones studied, is low. It appears that reasons other than liphophilicty may be responsible for CNS reactions (8).

The decrease in time spent in open arms of elevated plus-maze by putative anxiogenic agents is believed to be due to their actions on GABA-benzoidiazepine receptor complex (9). Inhibition of GABA binding to the GABA receptor, resulting in general excitation of CNS, may be the underlying mechanism of the CNS adverse phenomena produced by fluoroquinolones (10, 11, 12, 13). The central nervous system stimulating effect of ofloxacin can be reverted by co-administration of benzodiazepine agonist midazolam (11). Also the epileptogenic activity of norfloxacin is suppressed by muscimol and diazepam, which are agonists for the $GABA_A$-benzodiazepine receptor complex, but not by baclofen, a $GABA_B$ receptor agonist (10). A similar mechanism may be involved in the anxiogenic activity of the fluoroquinolones.

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