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Anxiogenic and proconvulsant effect of gatifloxacin in mice

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Abstract

The present study was performed to assess the neurological and neurobehavioural effects of gatifloxacin after its oral administration in two doses: 25 and 50 mg/kg for 7 days and 14 days in mice. The neurobehavioural parameters used for the short-term study (×7 days) were pentylenetetrazole-induced seizure, forced swim test, elevated plus-maze, spontaneous alternation behaviour and rota-rod tests. However, only pentylenetetrazole-induced seizure and rota-rod tests were performed in long term (×14 days) study. The results showed proconvulsant effect of gatifloxacin (50 mg/kg) in pentylenetetrazole-induced seizure test after both short- and long-term administration studies. Gatifloxacin in both doses showed an anxiogenic effect. However, in both doses, it did not show any effect on memory and mood as the drug did not show any effect in alternation behaviour and forced swim tests. In the long term study, gatifloxacin in 50 mg/kg, p.o. produced grip impairing effect only after 14 days of administration. These results reveal that gatifloxacin possesses proconvulsant and anxiogenic effects but it does not have an effect on mood and memory. Besides, long term administration of gatifloxacin for 14 days was found to reduce grip strength indicating its movement impairing effect in mice.

Keywords: Gatifloxacin; Neurological effects; Anxiety

1. Introduction

Fluoroquinolones are one of the widely prescribed groups of antimicrobial drugs. Although these drugs have demonstrated low incidence of side effects, several reports indicate central nervous system (CNS) toxicity in the form of headache, dizziness, tiredness, nightmares, confusion, insomnia and anxiety in 1–7% of treated patients. Other studies have described severe hallucinations, agitation, restlessness, depression and convulsions as manifestations of CNS toxicity of fluoroquinolones (Christ, 1990; Galatti et al., 2005; Thomas, 1994). However, convulsions appear to be the most severe adverse effect of fluoroquinolones in patients with underlying CNS disease and in patients who were concurrently treated either with certain nonsteroidal antiinflammatory agents or theophylline (De Sarro et al., 1997; Owens and Ambrose, 2005; Schmuck et al., 1998; Simpson and Brodie, 1985). The proconvulsant and epileptogenic effects have been observed with quinolones such as ciprofloxacin, ofloxacin, norfloxacin, pefloxacin and some newer agents, like levofloxacin, trovafloxacin and sparfloxacin in clinical as well as experimental studies (Akahane et al., 1993; Anastasio et al., 1988; Bharal et al., 2006; Janknegt, 1990; Lucent et al., 1988; Melvani and Speed, 2000; Rewari and Prabhu, 1999; Yamamoto et al., 1998). Certain quinolones like ciprofloxacin, gatifloxacin and pefloxacin have been found to cause psychosis in some patients receiving them (Hesslinger et al., 1996; Mulhall and Bergmann, 1995; Satyanarayana and Campbell, 2006; Reeves, 2007). Levofloxacin and sparfloxacin have been shown to possess anxiogenic potential in animal studies (Bharal et al., 2006; Erden et al., 2001).

Fluoroquinolones have also been shown to be associated with tendinopathy and arthropathy in younger patients, receiving these agents (Khaliq and Zhanel 2003; Mc Ewan and Davey, 1988; Mc Garvey et al., 1996). The first case of tendon rupture by ciprofloxacin was reported in 1987 (Mc Ewan and Davey, 1988). There is experimental evidence suggesting movement impairing effects with sparfloxacin, fleroxacin, pefloxacin, lomefloxacin, levofloxacin, ofloxacin in rodents. (Bharal et al., 2006; Kashida and Kato, 1997).

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Gatifloxacin is amongst the newer generation of fluoroquinolones which have good activity against gram negative organisms. Clinically it has been reported to produce nausea, dizziness, headache, insomnia, agitation and anxiety (Perry et al., 1999). Further, gatifloxacin was also shown to cause seizures in one patient (Marinella, 2001; Quigley and Lederman, 2004). However, experimental evidence is still needed to study its neurological and neurobehavioural effects.

In the present study we investigated the neurological and neurobehavioural effects of gatifloxacin on experimental models of seizures, anxiety, depression and cognition in mice. Rota-rod test has also been included to evaluate the effect of this agent on musculoskeletal system.

2. Materials and methods

2.1. Animals

Healthy Swiss albino mice of either sex weighing 24–35 g were used. The animals were procured from the Central Animal House, University College of Medical Sciences, Delhi. Animals were housed in groups of 6–8 per cage with free access to pellet diet and water. The experiments were performed at day time between 9:30 a.m. and 3:30 p.m., since circadian rhythm has not been reported to affect the measure of anxiety (Beeler et al., 2006; Bharal et al., 2006). The animals were taken care of in accordance with the guidelines prepared by Indian National Science Academy, India. The study was duly approved by the Institutional Animal Ethics Committee, University College of Medical Sciences, Delhi.

2.2. Drugs and dosing schedule

Gatifloxacin tablets (Gatimac) were purchased from the market. Pentylenetetrazole (Sigma, USA) was utilized in the study. The tablets were crushed and suspended in distilled water using carboxymethylcellulose (C.M.C.). Gatifloxacin was administered in dose of 25 and 50 mg/kg, orally. The control animals received 1% carboxymethylcellulose as vehicle in a dose of 10 ml/kg, p.o. The doses were calculated from the corresponding human doses (200 mg and 400 mg, respectively) commonly used for various infections (Perry et al., 1999). The short term and long term administration of gatifloxacin was performed for 7 days and 14 days, respectively. All test parameters were performed only after 7-days administration of gatifloxacin whereas pentylenetetrazole seizure and rota-rod tests were conducted in 14-days administration study. The observations were made after 45 min. (time of peak effect).

2.3. Pentylenetetrazole-induced seizures

Pentylenetetrazole was used in a dose of 45 mg/kg, i.p. This was the dose that produced clonic seizures in all the animals without mortality. Gatifloxacin was administered 1 h prior to pentylenetetrazole administration. The latency to myoclonic jerks was observed immediately after the proconvulsant drug injection for a period of 30 min (Bharal et al., 2006).

2.4. Elevated plus-maze

The maze was constituted of wood, painted gray and contained a central platform (8 × 8 cm) from which radiated four symmetrical arms (16 cm long × 5 cm wide, 10 cm walls). The two opposite arms were covered with plastic roof to assess effects on anxiety. The maze was elevated to a height of 25 cm. The mice were placed individually in the centre of the maze, head facing towards open arm. The number of entries in open and closed arms and time spent in open and closed arms, respectively were recorded for a period of 6 min (Pellow, 1985).

2.5. Forced swim test

Briefly, mice were forced to swim for 15 min in a bucket of height 45.5 cm, diameter 22 cm at the base containing fresh water (temperature 22 ± 2 °C) up to a height of 30 cm. This constituted the 'pretest session.' After 24 h, each animal was re-exposed to the swimming condition in a similar environment for a period of 6 min, 'Test Session.' The animal's vigorous attempts to escape were interspersed with bouts of immobility signifying 'behavioural despair.' Duration of immobility was measured for the period of test session, i.e. 6 min. The duration of immobility of treatment groups was compared with control group (Porsolt et al., 1997).

2.6. Spontaneous alternation behavior on plus-maze

The maze used to assess anxiety was also used to assess the cognitive functions with some modifications, i.e. all arms were side walled (16 × 5 × 10 cm) but had no roof. After being placed in the central platform, mice were allowed to traverse the maze freely for 6 min. The number and sequence of entries in different arms were recorded. An alternation was defined as entry into four different arms on overlapping quintuple sets. Five consecutive arm choices within the total set of arm choices made up a quintuple set. A quintuple set consisting of arm choices A, B, A,

Table 1
Effect of short term (7 days) and long term (14 days) administration of gatifloxacin on PTZ (50 mg/kg, i.p.) induced convulsions in mice

Group no.	Treatment (*n*)	Dose (per kg, oral)	Latency to myoclonic jerks (s)
7 days administration			
I	Vehicle C.M.C. 1% (6)	10 ml	275.7 ± 14.6
II	Gatifloxacin (6)	25 mg	237.0 ± 11.6
III	Gatifloxacin (6)	50 mg	177.8 ± 16.6[a]
14 days administration			
IV	Vehicle C.M.C. 1% (6)	10 ml	278.6 ± 14.6
V	Gatifloxacin (6)	25 mg	151.8 ± 6.7[a]
VI	Gatifloxacin (6)	50 mg	113.8 ± 11.9[a]

Values are mean ± S.E.M.
n: Number of animals.
[a]$P < 0.01$ vs Control (ANOVA followed by Dunnett's 't' test).
C.M.C. — carboxymethyl cellulose.