**Scholars Academic Journal of Pharmacy (SAJP)** **ISSN 2320-4206 (Online)**
**Sch. Acad. J. Pharm., 2016; 5(2): 20-26** **ISSN 2347-9531 (Print)**

(An International Publisher for Academic and Scientific Resources)
www.saspublisher.com

## Original Research Article

# A Study to Evaluate Proconvulsive Effect of Ofloxacin in Mice

**Kurle DG[1], Bagle TR[2], Satpute SM[3], Deshmukh YA[4]**

[1] Associate Professor, Dept of Pharmacology & Therapeutics, Seth GS Medical College & KEM Hospital, Mumbai 400012.

[2] Assistant Professor, Dept of Pharmacology, Rajiv Gandhi Medical College, Thane 400605.

[3] Assistant Professor, Dept of Pharmacology, TN Medical College, Mumbai 400008.

[4] Professor & Head, Dept of Pharmacology, MGM Institute of Health Sciences, Navi Mumbai 410209.

***Corresponding author**
Dr. D.G. Kurle
Email: dgkurle@yahoo.com

**Abstract:** The study was carried out to evaluate Proconvulsive effect of ofloxacin on electro convulsion & chemo convulsion and also to see its effect on locomotor activity in mice. The animals were given either saline (0.2 ml) or ofloxacin (25 mg/kg) intraperitoneally (i.p.) and the effect on spontaneous locomotor activity and maximal electroshock induced seizures (MES) was recorded. The mice were also given single & multiple doses of saline (0.2 ml i.p) or ofloxacin (25 mg/kg i.p.) and then they were subjected to sub convulsive doses of pentylenetetrazole (40 mg/kg i.p.) or picrotoxin (1 mg/kg i.p.) or strychnine (0.5 mg/kg i.p.). In results-the ofloxacin did not change the spontaneous locomotor activity or duration of tonic extension of hind limb of MES induced seizure significantly as compared to control group. Mortality was more in ofloxacin group after MES than the control group (30% vs 20%). No convulsions or jerky movements were seen after giving convulsants during single as well as multiple dose studies. Also no deaths were seen during subsequent 24 hours. The results indicate that ofloxacin may not have proconvulsant effect although higher doses of ofloxacin or other fluoroquinolones may be having this kind of adverse effects.
**Keywords:** Fluoroquinolones, convulsion, locomotor activity, Maximal electroshock seizure.

## INTRODUCTION

Fluoroquinolones are a one of the popular class of antimicrobial agents prescribed in a variety of infections caused by gram negative, gram positive and atypical bacteria. The antimicrobial activity of fluoroquinolones is due to the inhibition of bacterial DNA gyrase [1].Common adverse effects of fluoroquinolones ranges from mild reactions like headache, nausea, vomiting, diarrhea, to severe ones like photosensitivity, visual disturbances, insomnia, hepatic and renal insufficiency, tendinopathy, prolongation of QT interval, neurotoxicity and neuropathy [1, 2]. Seizures are almost always associated with a predisposing factor such as brain tumor, anoxia or metabolic imbalance, or concomitant therapy with interacting agents like theophylline or the nonsteroidal anti-inflammatory drugs [3, 4].

Effects on CNS of quinolones in animals include decreased locomotor activity and roto rod performance, along with minimal effects on general behaviour. After quinolone use in humans, seizures, depression, anxiety, euphoria, somnolence and insomnia have been reported [4]. Fluoroquinolones inhibit binding of gamma amino butyric acid (GABA) to receptors in rat brain synaptic membranes. For some nonquinolones agents (and perhaps the fluoroquinolones also) such inhibition appears to correlate with epileptic potential of drug [5]. The molecular mechanism by which fluoroquinolones cause seizures in humans and animals, however, is not well understood [6].

Most of the case reports of seizures contain minimal details, and the patient's concurrent medications could have directly caused seizure activity [7]. Furthermore, the association cannot be established with certainty by a rechallenge due to ethical consideration.

Hence the present study was conducted to evaluate proconvulsive activity of one of the commonly used fluoro quinolone, ofloxacin, on electro convulsion and chemo convulsion and also to see its effect on locomotor activity in mice and correlate the same if possible with relative incidences of seizures occurring clinically.

## MATERIALS AND METHODS

The animal experiments were carried out in accordance with the guidelines set by the "Committee for the Purpose of Control and Supervision of

Experiments on Animals" after the Institutional Animal Ethics Committee of T. N. Medical College & B.Y.L. Nair Ch. Hospital approved the study.

***Animals***

Adult albino mice weighing between 20 to 30 gms and of either sex were used for the study. These mice were maintained at room temperature in a well-ventilated and clean animal house. Animals had free access to food and water during the course of the experiment. The animals were from the same stock and were housed in the animal house of the department of pharmacology of T. N. Medical College in Mumbai.

**Drugs**

Ofloxacin injection (Commercial name - Of lox) prepared and marketed by Cipla Pharmaceuticals was used in a dose 25 mg/kg given intraperitoneally in mice.

***Experimental Groups and Drug Treatment***

**A) Spontaneous Locomotor Activity**

Method used in study

The effect of ofloxacin and saline on spontaneous locomotor activity was registered with Photoactometer (INCO, India) with automatic counting of animal movements on the cage floor. Photocells located on the wall directly opposite each photo-beam were activated when the animal interrupted the beam and interruption of any beam was recorded as an activity score. Two groups of mice (n=10) were administered with either normal saline (0.2 ml i.p or ofloxacin (25mg/kg i.p.) respectively.

Group I: Normal saline 0.2 ml i.p.
Group II: Ofloxacin 25 mg/kg i.p.

One mouse was kept at a time in the photoactometer and locomotor activity was recorded for 5 mins. Baseline activity was recorded just before saline/ofloxacin injection and final activity was recorded 30 mins after respective injection.

**B) Electro convulsion**

Method used in study:

The method used in this study was Maximal Electroshock induced seizures (MES) in mice. This method was preferred because it is reliable, reproducible and the end point of this experiment was duration of tonic extension of hind limb is well defined and consistent. It is a relatively simple method for screening anticonvulsant and hence commonly employed [8]. Techno convulsiometer was used to induce MES convulsions. The electric current for producing the convulsion was delivered 30 mins after giving saline or ofloxacin to the mouse using ear clip electrode. A 60 mA current was delivered trans auricularly for 0.2 seconds in mice via ear clips electrode. The same method has been used in few previous studies [9, 10]. The animals were randomly divided into two groups (Group no. III & IV), each comprising of ten animals and were given treatment as under.

Group III: Normal saline 0.2 ml i.p.
Group IV: Ofloxacin 25 mg/kg i.p.

The parameters were observed after giving MES were duration of tonic extension of hind limb in seconds and number of deaths in each group.

**C) Chemo convulsion**

Chemicals used in study

Three convulsants having different cellular mechanisms of CNS excitation were used in sub convulsive doses.

1) Strychnine -Strychnine hydrochloride was obtained from Sigma chemicals. Strychnine 50 mg powder was weighed on a single pan Stanton balance. The powder was dissolved in 1 liter of distilled water to form a stock solution containing 0.05 mg/ml of strychnine HCL.

2) Pentylenetetrazole – It was obtained from Sigma chemicals. Pentylenetetrazole 400 mg powder was weighed on a single pan Stanton balance. The powder was dissolved in 100 ml of distilled water to form a stock solution containing 4 mg/ml of Pentylenetetrazole.

3) Picrotoxin – It was obtained from Sigma chemicals. Picrotoxin 40 mg powder was weighed on a single pan Stanton balance. The powder was dissolved in 400 ml of distilled water to form a stock solution containing 0.1 mg/ml of Pentylenetetrazole.

Method used in study

The development of clonic seizures in ofloxacin treated mice with sub convulsive dose of strychnine; picrotoxin or pentylenetetrazole was taken as criterion of proconvulsant activity [11]. Mice were randomly allocated to following six groups each consisting of ten animals and 30 mins after being treated with either saline or ofloxacin, they received intraperitoneal injection of 0.5 mg/kg of strychnine (Group no. V and VI) or 1 mg/kg of picrotoxin (Group no. VII and VIII) or 40 mg/ kg of pentylenetetrazole (Group no. IX and X) i.e. in sub convulsive doses.

Phase I (single dose study)
Group V: Normal saline 0.2 ml i.p. followed by Strychnine 0.5 mg /kg i.p after 30 mins
Group VI: Ofloxacin 25 mg/kg i.p. followed by Strychnine 0.5 mg /kg i.p. after 30 mins
Group VII: Normal saline 0.2 ml i.p followed by Picrotoxin 1 mg/kg i.p. After 30 mins
Group VIII: Ofloxacin 25 mg/kg i.p. followed by Picrotoxin 1 mg/kg i.p. after 30 mins
Group IX: Normal saline 0.2 ml i.p followed by Pentylenetetrazole 40 mg/kg i.p. after 30 mins

Group X: Ofloxacin 25 mg/kg i.p. followed by Pentylenetetrazole 40 mg/kg i.p. after 30 mins.

All animals were observed for one hour after injecting convulsants for following parameters like time (in minutes) to the onset of the first proconvulsive jerks, number of jerky movements, time taken to first convulsion, number of convulsions in the first hour, duration of longest lasting convulsion in seconds. Also number of deaths at the end of one hour of injection and subsequent 24 hrs were recorded.

Phase II (multiple dose study)

Multiple dose study was done only for chemo convulsion. A wash out period of 10 days was given after completion of single dose study. Respective drugs (normal saline and ofloxacin i.p.) were then administered to the animals of Group no V to Group no X twice daily for 7 days. After this course of treatment, strychnine, picrotoxin or Pentylenetetrazole were administered to induce chemo convulsion and observations were recorded as in phase I study.

**Analysis of Data:**

The parametric data of spontaneous locomotor activity and duration of tonic extension of hind limb were analyzed by unpaired t test. Percentage of deaths were analysed using Fisher's exact test. In all the tests, the criterion for statistical significance was $p < 0.05$.

## RESULTS

**A) Effect of Saline & Ofloxacin on spontaneous locomotor activity in mice (Table 1 & Figure 1)**

In control group, spontaneous locomotor activity (per 5 mins) reduced from baseline level of 357.8 ± 43.83 (Mean ± SD) to 277.4 ± 35.23 and in ofloxacin group it reduced from 476 ± 37.14 to 297 ± 32.03. There was greater reduction in spontaneous locomotor activity in ofloxacin group (178 ± 39.20) than that of control group (80.4 ± 27.74) but the difference was not statistically significant.

**Table 1: Effect of Saline & Ofloxacin on spontaneous locomotor activity**

| **Parameters (per 5 min)** | **Control (0.2 ml saline i.p)** | **Ofloxacin (25 mg/kg i.p.)** |
|---|---|---|
| Mean baseline activity | 357.8 ± 43.83 | 476 ± 37.14 * |
| Mean final activity | 277.4 ± 35.23 | 297 ± 32.03 |
| Mean difference in activity | 80.4 ± 27.74 | 178 ± 39.20 ** |

SD is standard deviation, * p =0.054, ** p =0.056 (Unpaired t test).

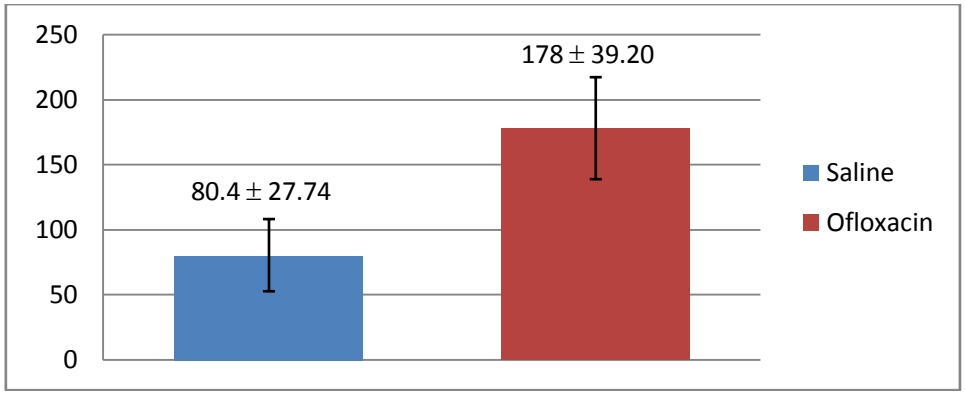


**Fig-1:Mean difference in locomotor activity (per 5 mins)**

**B) Effect of Saline & Ofloxacin on Maximal Electroshock induced Seizure (Table 2, Figure 2)**

The mean duration of tonic extension of hind limb after MES induced convulsion was slightly more (14.7 ± 0.83 s; Mean ± SD) than that of control group (13.89 ± 0.63) but the difference was not statistically significant. Also there was more number of deaths (3) in the ofloxacin group as compared to two deaths in the control. But again the difference was not statistically significant.

**Table 2: Effect of Saline & Ofloxacin on Maximal Electroshock induced Seizure**

| **Parameters** | **Control (0.2 ml saline)** | **Ofloxacin (25 mg/kg)** |
|---|---|---|
| Mean duration of hind limb extension in secs | 13.89 ± 0.63 | 14.7 ± 0.83 * |
| No of deaths (out of 10) | 2 | 3 ** |

SD is standard deviation, p = 0.45* (Unpaired t test), p =1** Fishers exact test

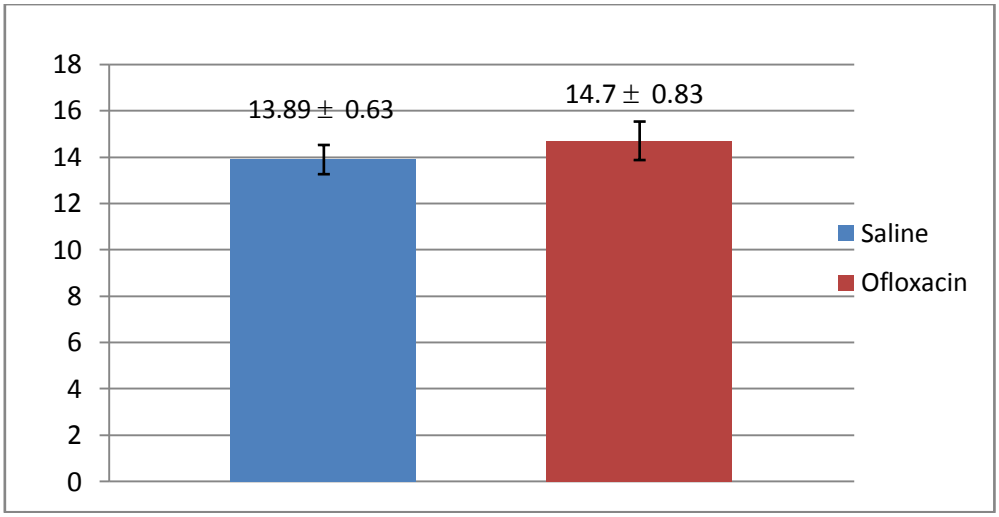


**Fig-2: Mean duration of hind limb extension (secs)**

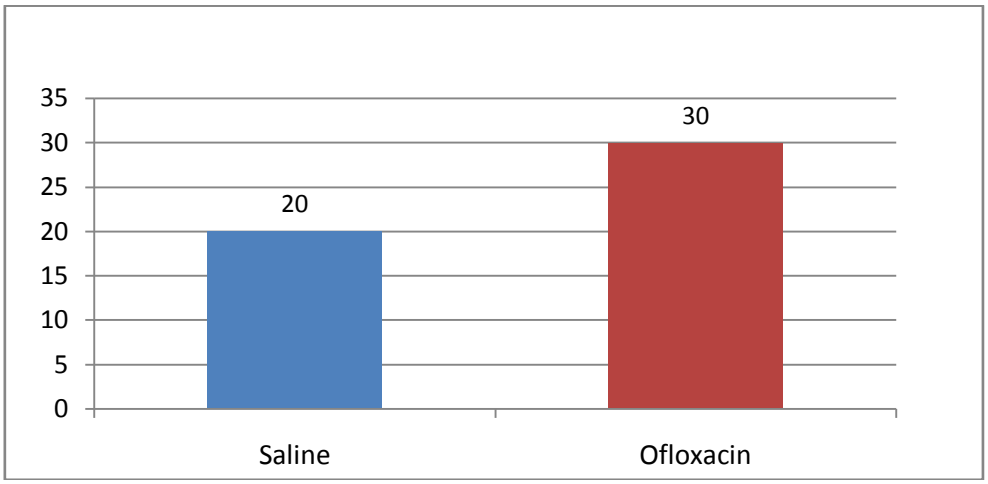


**Fig-3: No of deaths (%)**

**C) Effect of saline and ofloxacin on chemo convulsion**

There were no convulsions or jerky movements were observed during 1 hour observation period in control and ofloxacin groups on chemonvulsion induced with Strychnine 0.5 mg/kg, Picrotoxin 1 mg/kg or Pentylenetetrazole 40 mg/ kg in single as well as multiple dose studies. No deaths were recorded in subsequent 24 hours.

## DISCUSSION

Neurotoxic potential of fluorqinolones have been demonstrated by many preclinical and clinical studies. Patients have reported headache, insomnia, irritability, dizziness, restlessness, convulsions, hallucinations, psychotic episodes etc. There is black box warning for fluoroquinolones and they should be avoided in patients suffering from disorder affecting central nervous system. But many case studies have also reported concomitant administration of drugs like theophylline along with fluoroquinolones [12, 13, 14]. There are reports suggesting a higher rate of seizures in patients with ofloxacin which is one of the widely used fluoroquinolones as compared to others. Ofloxacin has higher CNS penetration but lower affinity to GABA as compared to other fluoroquinolones [15, 16]. Some fluoroquinolones have shown pro-convulsant activity in the in vitro and in vivo animal experiments whereas other published reports have failed to show this pro-convulsant activity.

In the present study, an attempt was made to find out if ofloxacin has proconvulsant activity and what may be the underlying mechanism of it. Ofloxacin given in single dose of 25 mg/kg intraperitoneally did not reduce the spontaneous locomotor activity significantly as compared with the baseline or with the control group (Table 1 & Figure 1). The first measure of animals' activity is the rate of habituation to a novel environment. Thus, during prolonged exposure to a new environment, animals spend progressively less time in exploration. This could be the reason behind the decrease in the activity in both the group [17]. There are studies which showed that levofloxacin, which is an optical isomer of ofloxacin and other fluoroquinolones either decreased or did not affect locomotor activity and rotarod performance in animals. One study found no significant change in the locomotor activity of juvenile

and adult rats after 600 mg/kg dose of ofloxacin for five days. This shows that ofloxacin does not have any significant effect of spontaneous locomotor activity [18, 19].

In the present study, the duration of tonic extensor phase was slightly more in the ofloxacin group as compared to control group on maximal electroshock induced seizures, but the difference was not statistically significant. Similarly there were 3 deaths in ofloxacin treated group as compared to 2 in control group. Different studies showed that ofloxacin, sparfloxacin and moxifloxacin had no statistically significant effect on tonic extensor phase of MES induced seizure, but ciprofloxacin and pefloxacin & Levofloxacin (25 mg/kg given i.p.) had significant worsening effect in mice & rats [20, 21]. On the other hand, one study reported increased duration of tonic hind limb extension with ciprofloxacin (25 & 50mg/kg) but decrease in the duration with ofloxacin (25 & 50 mg/kg) in dose dependent manner with respect to the control group in wistar rats [22].

For chemo convulsion, the study was carried out in two phases, single close and multiple dose studies. Multiple doses were incorporated to simulate the situation in clinical practice where drugs are given for prolonged period of time. Between two phases a washout period of 10 days was given. No convulsions or jerky movements were observed during 1 hour observation period in either groups on chemo convulsion induced with sub convulsive doses of strychnine, picrotoxin or pentylenetetrazole. Also no deaths were recorded in subsequent 24 hours. In other studies, ofloxacin (20 or 80 mg/kg i.p) have shown to increased the incidence of clonic convulsions induced by sub convulsive doses of pentylenetetrazole. This effect however was only significant in the higher dose [23]. But Levofloxacin (25 mg/kg given i.p.) didn't show enhancing effect on Pentylenetetrazole induced convulsions [21].

Structure toxicity relationship shows that the C-7 substituent on the quinolone nucleus, particularly pyrrolidine or piperazine, plays an important role in the CNS effects of these compounds [24]. Quinolones containing 7- piperazine (e.g., ciprofloxacin, norfloxacin) and those containing 7-pyrrolidine (e.g., tosufloxacin and clinafloxacin) have increased epileptogenic potential while substituted compounds containing 7- piperazinyl– or 7-pyrollidinyl (e.g., levofloxacin) are associated with reduced seizure-causing potential. Gemifloxacin, levofloxacin, and moxifloxacin lack the specific structure-toxicity relationships noted to induce seizures [25]. The nature of C-7 substituent may also determine the interaction with non-steroidal anti-inflammatory drugs (NSAIDs) and theophylline which can potentially increase the chances of seizures. Other receptors possibly involved in the CNS excitatory effects include N-methyl-D-aspartate, adenosine and amino acid receptors while effects on dopamine and opioid receptors has also been suggested [26].

The lipophilicity which determines CNS penetration of fluoroquinolones does not always correlate with the potential for epileptogenicity. In contrast to ciprofloxacin, ofloxacin has an increased CNS permeability of 50% of the serum concentration, though less cases of neurotoxicity have been reported for ofloxacin than for ciprofloxacin [12, 27]. The electrophysiological determination of field potentials in the CA1 region of the rat hippocampus slice was done to assess the excitatory potential of fluoroquinolones, which might be predictive for their neurotoxic potency in vivo. They increased the population spike amplitude in a concentration-dependent manner, and the resulting excitatory potency was highly dependent on the chemical structure, these investigations pointed to the N-methyl-D-aspartate receptor as the probable target of the fluoro quinolone effects [28].

In another study in humans in which the etiology of the effects to the CNS of selected fluorinated quinolones was assessed by positron emission tomography, ciprofloxacin treated subjects showed a significant decrease in cerebral blood flow compared to baseline as well as to temafloxacin and placebo treatment groups [29].

In vitro, epileptic potential is usually assessed by determination of the affinity for γ-amino butyric acid A (GABA A) receptors. However, the extrapolation of these results to the clinical setting seems very difficult for several different reasons. Because there are other mechanisms are also involved apart from GABA inhibition. And because the affinity of quinolones alone for the GABA A receptors is actually relatively low, and to observe significant binding, experiments have to be conducted in the presence of a nonsteroidal anti-inflammatory derivative, usually biphenyl acetic acid. So the results of GABA binding experiments could therefore only be extrapolated, to a situation in which quinolones are given together with NSAID [30]. Secondly, in vitro experiments, including new approaches such as the use of the Xenopus oocyte translation system of exogenous mRNA do not take into consideration the pharmacokinetic characteristics of drugs, in particular, their ability to reach the receptors at the central level which may vary considerably from one quinolone to another [31].

## CONCLUSION

From the present study it can be concluded that ofloxacin does not have significant proconvulsant activity in mice as it did not show such effect on spontaneous locomotor activity, electro convulsion & chemo convulsion, although higher doses of ofloxacin or other fluoroquinolones may be having such kind of effects. It is worth noting that all three convulsants used

have distinct cellular mechanisms of CNS excitation. However these conclusions are drawn in rodent models of epilepsy and have to be supported by substantial proof in actual human trials. There is conflicting data about whether ofloxacin has proconvulsive effect and about possible explanation of this proconvulsive action. Thus further research is necessary to exactly pinpoint role of ofloxacin in epilepsy.

**REFERENCES**


1. LL Chabner BA, Knollmann BC; Sulfonamides, Trimethoprim-Sulfamethoxazole, Quinolones, and agents for urinary tract Infections. In: Goodman & Gilman's the pharmacological basis of therapeutics. 12th Ed. The McGraw-Hill Companies Inc; 2011; 1470-6.
2. Owens Jr, Ambrose; Antimicrobial safety: focus on fluoroquinolones. Clin Infect Dis 2005; 41 (2):144-57.
3. Davies BL, Maesen FPV; Drug interaction with quinolones, Rev Infect Dis 1989; (suppl 5): S1083-90.
4. Christ W, Lehner T, Ulbrich B; Specific toxicological aspects of the quinolones. Rev Infect Dis 1988; 10(suppl 1):141-6.
5. Tsuji A, Sato H, Kume Y, Tamai I, Okezaki E; Inhibitory effects of quinolone antibacterial agents on γ-amino butyric acid binding to receptor sites in rat brain membranes. Antimicrob Agents Chemother 1988; 32:190–194.
6. Christ W, Lehnert T; Toxicity of the quinolones In: Siporin C, Hefietz CL, Domagala JM; The new generation of quinolones New York, Marcel Dekker, 1990: 165-87.
7. Bercault N, De Masure M, Berihamoa CL, Gueveler C; Seizures in the course of prolonged treatment with ofloxacin. Rev Med Interne 1993; 14:194.
8. Toman J.E, Everett G.M; Anticonvulsants. In: Laurence DR and Bacharach AL, editors. Evaluation of drug activities: pharmacometrics. London: Academic Press, 1964; 287-299.
9. Srivastava K., Gupta YK; Aspirin modulates the anticonvulsant effect of Diazepam and Sodium Valproate in penetylenetetrazole and Maximal Electroshock induced seizures in mice. Indian J Physiol Pharmacol 2001; 45: 475-480.
10. Manocha A, Sharma K, Medirata, P; Tramadol, a centrally acting opioid: Anticonvulsant effect against maximal electroshock seizures in mice. Indian J Physiol Pharmacol 1998a; 42: 407-411.
11. Turner R.A; Anticonvulsants. In: Turner RA, editor. Screening methods in pharmacology. New York: Academic Press, 1965; 164-172.
12. Wolfson J.S; Overview of fluoroquinolones safety. Am J Med 1991; 91(supp 6A): 153-61.
13. Matrindale-The Complete Drug Reference. 36th Edition. Pharmaceutical Press: London; 2009.
14. Covelli GD, Knodel AR, Heppner BT; Predisposing factors to apparent theophylline induced seizures. Ann Allergy 1985; 54: 411-5.
15. Leroy O, Beuscart C, Sivery N, Senneville E, Mouton Y; Efficacy and tolerance of intravenous ofloxacin. Presse Med 1989; 18:2050-4.
16. Walton GD, Hon JK, Mulpur TG; Ofloxacin-induced seizure. Ann Pharmacother. 1997 Dec; 31(12): 1475-7.
17. Luszczki JJ, Czuczwar M, Kis J, Krysa J, Pasztelan I, Swiader M, Czuczwar SJ; Interactions of lamotrigine with topiramate and first-generation antiepileptic drugs in the maximal electroshock test in mice: an isobolographic analysis. Epilepsia 2003; 44:1003-13.
18. Erden BF, Ulak G, Yildiz F, Utkan T, Ozdemirci S, Gacar N; Antidepressant, anxiogenic, and antinociceptive properties of levofloxacin in rats and mice. Pharmacol Biochem Behav. 2001; 68(3): 435-41.
19. Thiel R, Metzner S, Gericke C, Rahm U, Stahlmann R; Effects of fluoroquinolones on the locomotor activity in rats. Arch Toxicol. 2001; 75(1): 36-41.
20. Rewari S, Prabhu S; A comparative study of proconvulsive potential of fluoroquinolones. Indian journal of pharmacology 1999; 31: 29-32.
21. Kumar AA , Kumar PR, Reddy KP, Sujith TR, Pathapati RM; Proconvulsive profile of Fluoroquinolones - an experimental Study with clinical co-relations Int. J. Pharm. Med. & Bio. Sc. 2013; 2(2): 23-30.
22. Aravind A, Gopalakrishna HN, Kateel R, Rai M, Shridhar D, D'souza RA; Comparative study on the effect of fluoroquinolones in experimental seizures on wistar rats: An acute study. Int J Pharm Sci 2015; 7 (8): 305-308.
23. Enginar N, Eroglu L; The effect of ofloxacin and ciprofloxacin on pentylenetetrazole-induced convulsions in mice. Pharmacol Biochem Behav. 1991; 39(3): 587-9.
24. Domagala JM; Structure activity and structure side effect relationship for the quinolone antibacterials. J Antimicrob Chemother 1994; 33: 685-706.
25. Thomas RJ; Neurotoxicity of antibacterial therapy. South Med J. 1994; 87(9): 869-74.
26. Takayama S, Hirohashi M, Kato M, Shimada H; Toxicity of quinolone antimicrobial agents. J Toxicol Environ Health 1995; 45(1): 1-45.
27. Grill MF, Maganti RK; Neurotoxic effects associated with antibiotic use: management considerations. Br J Clin Pharmacol 2011; 72 (3): 381–393.
28. Schmuck G, Schürmann A, Schlüter G; Determination of the Excitatory Potencies of Fluoroquinolones in the Central Nervous System by an In Vitro Model. Antimicrobial Agents and Chemotherapy, 1998; 42 (7): 1831-1836.
29. Bednarczuk EM, Green JA, Nelson AD, *et al.;* Comparison of the effect of ciprofloxacin or

placebo on cerebral blood flow, glucose and oxygen metabolism in healthy subjects via positron emission tomography. Clin Pharmacol Ther 1991; 50:165-71.

30. Akahane K, Sekiguchi M, Une T, an`d Osada Y; Structure-epileptogenicity relationship of quinolones with special reference to their interaction with γ-amino butyric acid receptor sites. Antimicrob Agents Chemother 1989; 33:1704–1708.
31. Kawakami J, Yamamoto K, Asanuma A, Yanagisawa K, Sawada Y, Iga T; Inhibitory effect of new quinolones on GABAA receptor-mediated response and its potentiation with felbinac in Xenopus oocytes injected with mouse-brain mRNA: correlation with convulsive potency in vivo. Toxicol Appl Pharmacol 1997; 145:246–254.