International Journal of Medicine and Medical Sciences ISSN 2167-0404 Vol. 8 (2), pp. 001-013, February, 2018.
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Full Length Research Paper

Evaluation of the effects of ciprofloxcin or gatifloxacin on neurotransmitters levels in rat cortex and hippocampus

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Accepted 07 July 2017

The objective of the present work is to study the possible role of neurotransmitters in the central nervous system (CNS) side effects due to the administration of ciprofloxacin (80 mg/kg body weight) and gatifloxacin (32 mg/kg body weight) in male albino rats for 3, 7 and 14 days.The frontal cortex of ciprofloxacin and gatifloxacin treated groups revealed decrease of glutamate, γ-aminobutyric acid (GABA), dopamine and serotonin levels and elevation of aspartate, asparagine, glycine, serine and norepinepherine levels and acetylecholinestrase (AChE) activities in a time related effect. In the hippocampus area, the results varied in each antibiotic where in ciprofloxacin treated groups, there is an elevation of asparagine, GABA, glycine, serine, taurine, norepinepherine and dopamine levels and a reduction of glutamate, aspartate and serotonin levels and AChE activities in a time related effect. In gatifloxacin treated groups, there is an elevation of glutamate, aspartate, asparagine, GABA, glycine, taurine and norepinepherine and reduction in the levels of dopamine and serotonin and the AChE activities. The histopathological examinations showed sever congestion with perivascular oedema in the blood vessels and capillaries of cerebral cortex as well as of the hippocampus. Overall, the data suggest that there is a shift in the balance between neurotransmitters towards increased production of excitatory potency in groups subjected to ciprofloxacin or gatifloxacin administration.

Key words: Ciprofloxacin, Gatifloxacin, Amino Acids, Monoamines, Acetylcholinesterase.

INTRODUCTION

Fluoroquinolones are among the most widely prescribed antibiotics especially for respiratory and urinary tract infections. They are generally regarded as safe drugs associated with mild gastrointestinal and central nervous system (CNS) symptoms (Jose et al., 2007; Becnel et al., 2009). Recent events have brought new attention to quinolone safety. Four quinolones have been withdrawn from the US market: temafloxacin, as a result of hemolysis, renal failure and hypoglycemia; trovafloxacin, as a result of hepatotoxicity; grepafloxacin, as a result of torsades de pointes; and sparfloxacin as a result of phototoxicity and torsades de pointes (Frothingham, 2005).

Ciprofloxacin remains amongst the safest of all antibiotics with remarkably few reports of serious reactions over a period of 15 years of use and more than 340 million prescriptions (Ball et al., 1999; Segev et al., 1999). Ciprofloxacin-associated seizures occur most commonly in patients with special risk factors that may

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Abbreviations: CNS, Central nervous system; **AChE,** acetylecholinestrase; **NODCAR,** National Organization for Drug Control and Research; **HPLC,** high performance liquid chromatography; **GABA,** γ-aminobutyric acid; **MES,** maximal electro shock.

cause accumulation of drug or that may decrease the threshold of epileptogenic activity (Kushner et al., 2001; Kisa et al., 2005). On the other hand, ciprofloxacin induced seizures in healthy patients (Darwish, 2008).

Gatifloxacin is one of the newer broad spectrum fluoroquinolones available and was approved by the US food and drug administration in December 1999. Ever since its release in the market, there have been numerous reports implicating gatifloxacin as a cause of dysglycemia. This prompted Bristol-Meyer Squibb Co. to list diabetes mellitus as a contraindication to gatifloxacin use in the US product labeling and Health Canada to issue an advisory against the use of gatifloxacin in patients with diabetes (Jose et al., 2007). Gatifloxacin showed to be equivalent to ciprofloxacin for the treatment of acute uncomplicated lower urinary tract infections (Naber et al., 2004).

In recent years, extensive *in vivo* and in vitro experiments have been performed in an attempt to explain the CNS side effects of quinolones sometimes observed under therapeutic conditions. These effects include like dizziness, restlessness, tremor, insomnia, hallucinations, convulsions, anxiety and depression. However, the molecular target or receptor for such effects is still not exactly known. Extensive toxicological and biochemical experiments have been performed to explain the CNS effects observed under therapeutic conditions (Akahane et al., 1993; De Sarro et al., 1999; De Sarro and De Sarro 2001; Arafa et al., 2004). According to Freitas et al. (2004) and Cavalheiro et al. (2006), seizure activity of quinis associated with a wide range of local biochemical changes, affecting various neurotransmitters (monoamines, amino acids).

Since *status epilepticus* is a life-threatening neurologic emergency which leads to neuronal degeneration of vulnerable brain regions, we decided to estimate the effect of antibiotics under investigation ciprofloxacin and gatifloxacin in concern with their previously investigated epileptogenic potential in the hippocampal and frontal cortical areas because the development of spontaneous seizures is characterized by paroxysmal activity initially localized in the hippocampal formation and spreading of paroxysmal activity from hippocampal to cortical recordings was demonstrated (Cavalheiro et al*.,* 1991).

The frontal cortex and hippocampus areas appeared to be important in the expression of early convulsive seizures (Kelly et al., 1999; Ang et al., 2006) in addition to the important functional association between cortical regions and the hippocampus in seizure propagation (Kelly et al., 2002). Also, the frontal cortex and hippocampus suggested playing a role in inducing convulsions by quinolones (Motomura et al., 1991).

The present study aims to throw light on the effect of either ciprofloxacin or gatifloxacin administration under therapeutic level in male albino rat on the concentrations of amino acid and monoamine neurotransmitters and acetylecholinesterase activities in the frontal cortex and hippocampus brain areas. The study aims to ascertain the effect of the two antibiotics administration for one, three, seven and fourteen days. Also the study extended to include the histopathological effect of the two antibiotics under investigation during the tested durations on cortical and hippocampal brain areas.

MATERIALS AND METHODS

Experimental animals

This study was carried out on one hundred eight adult male albino rats (*Rattus norvegicus*) with average body weight ranged 100g ± 20 g obtained from the Egyptian Institution of Serum and Vaccine (Helwan). The experiment conducted in the Department of Physiology in National Organization for Drug Control and Research (NODCAR). The male albino rats were housed in iron mesh cages with seven rats each. Clean sawdust was used to keep the animals dry and clean throughout the experimental periods. The experimental animals were allowed to acclimate under the laboratory conditions two weeks before the beginning of the experiments. The animals were kept under controlled temperature of 21°C and 12 h light/ 12 h dark cycle throughout the course of experiment. A commercial pelleted diet was used during the experiment and allowed with water *ad libitum*.

Drug

Ciprofloxacin (Cipro) ($C_{17}H_{18}FN_3O_3$•HCl•H_2O), manufactured by Bayer healthcare pharmaceuticals, ciprofloxacin hydrochloride tablets and Gatifloxacin (TEQUIN) ($C_19H_{22}FN_3O_4$•1.5 H_2O), manufactured by Bristol-Myers Squibb Company, The antibiotics were administered by gastric intubation technique daily for fourteen days. The administered doses calculated equivalent to the human therapeutic dose according to the Guidance for Industry and Reviewers (2002).

Experimental design

Animals were divided into three groups using random selection. The first group (n= 12 rats) were administered 2 ml of distilled water daily. The second group (n=48 rats) were administered 80 mg/100 g body weight ciprofloxacin dissolved in 2 ml water (cipro-treated rats). The gatifloxacin-treated rat groups (n=48 rats) were administered 32 mg/ 100 g body weight gatifloxacin dissolved in 2 ml water. At the end of the experimental periods 3, 7 and 14 days, twelve animals sacrificed after 12 h from the last dose administration by rapid decapitation. The brains were dissected out quickly weighed and cleaned. Four brains from each treated group served for the histopathological examination according to Banchroft et al. (1996) and the rest eight brains for the biochemical analysis. There is a single control group representing the control of the study.

The frontal cortex and hippocampus brain areas were separated and divided into two halves the first half served for acetylcholinesterase activity assay according to the modified of Ellman et al. (1961) method as described by Gorun et al. (1978) and the second half was homogenized in 75% high performance liquid chromatography (HPLC) methanol (1/10 weight/volume) using

a homogenizer surrounded with an ice jacket and the homogenates were used for the determination of the brain contents of amino acids using the precolumn PTC derivatization technique according to method of Heinrikson and Meredith (1984) and monoamines neurotransmitters according to method described by Pagel et al. (2000).

RESULTS

Data presented in Table 1 recorded the effect of ciprofloxacin or gatifloxacin on amino acid neurotransmitters in the frontal cortex and hippocampus of male albino rats. The data showed a significant decrease of glutamic acid concentration in the frontal cortex as a result of treatment with ciprofloxacin and gatifloxacin throughout the experimental periods as compared to control. In hippocampus, the ciprofloxacin treated groups showed a significant decrease after the 7^{th} and 14^{th} days of the experimental periods as compared with the control. On the contrary, gatifloxacin treated groups exhibited a significant increase at 0.05 levels in the 3^{rd} and 14^{th} day's groups as compared to control one.

As regard to frontal cortex aspartic acid concentration, ciprofloxacin treatment produced a significant increase ($P<0.05$) throughout the experimental durations and the maximum effect achieved after 14 days while, gatifloxacin treated groups exhibited significant decrease ($P<0.05$) from the 3^{rd} day of administration throughout the experimental durations as compared to the control value. In the hippocampus tissue data showed significant decrease of aspartate level at the 3^{rd} and 7^{th} day in ciprofloxacin administered groups, but after the 14^{th} day of drug administration, aspartate level was elevated restoring to some extent its control value. Gatifloxacin administered groups, on the other hand, exhibited significant increase at 0.05 levels from the 3^{rd} to the 14^{th} day groups as compared to control one.

Asparagine level increased significantly in ciprofloxacin and gatifloxacin administed groups till the last 14^{th} day as compared to the control value in the frontal cortex and hippocampus.

γ-aminobutyric acid (GABA) concentration decreased in the frontal cortex but increased in hippocampus significantly ($P<0.05$) as compared to the control level from the 3^{rd} day of either ciprofloxacin or gatifloxacin administered groups till the 14^{th} day post- administration.

Glycine concentration in the frontal cortex increased significantly ($P<0.05$) as compared to the control level from the 3^{rd} day of ciprofloxacin (Cip) administration till the end of the experimental periods, but it was increased significantly ($P<0.05$) only at the 14^{th} day as compared to the control level post gatifloxacin (Gati) administration. In the ciprofloxacin groups but only to the 7^{th} day in gatifloxacin ones.

Taurine level decreased significantly ($P<0.05$) post-ciprofloxacin administration for 7 doses and the continuity of the drug administration till the 14 days reflected insignificant increase in taurine level as compared to that of the control group in the frontal cortex but gatifloxacin administration showed only significant decrease at the last dose administered. In hippocampus, the data showed significant increase at the 3^{rd} and 14^{th} experimental periods post-ciprofloxacin administration in the taurine levels as compared to the control value. Gatifloxacin administration showed significant increase in the taurine level ($P<0.05$) in all treated groups as compared to control level.

The data in Table 2 recorded the effect of ciprofloxacin or gatifloxacin on monoamine neurotransmitters in the frontal cortex and hippocampus of male albino rats.

Norepinepherine level was significantly decreased ($P<0.05$) after the 3^{rd} dose of ciprofloxacin or gatifloxacin treatments as compared to the control level till the 14^{th} day administered groups in the frontal cortex. In contrast to that of the frontal cortex, norepinepherine concentration in hippocampus exhibited a significant increase in from the 3^{rd} till the 14^{th} day's ciprofloxacin or gatifloxacin administered groups as compared to the control concentration.

Dopamine contents showed significant decreases ($P<0.05$) in the frontal cortex at the 7^{th} and 14^{th} days of either ciprofloxacin or gatifloxacin administration as compared to the control value. In the hippocampus, the data showed significant increase in dopamine level after the 3^{rd} day till the 14^{th} day of ciprofloxacin administration but gatifloxacin administration exhibited a significant decrease only at the 7^{th} dose administered.

As regard to the frontal cortex serotonin level, ciprofloxacin administration showed significant decrease ($P<0.05$) in its level after the 3^{rd} and 7^{th} doses as compared to the control one and increased significantly after the 14^{th} day of experimental duration. Gatifloxacin administration showed significant decrease in the serotonin level from the 3^{rd} till the 14^{th} day administered group as compared to the control value.

In the hippocampus, serotonin concentration showed significant decrease from the 7^{th} till 14^{th} day's ciprofloxacin administered groups as compared to the control concentration. In the same trend, gatifloxacin administration exhibited significant decrease at 0.05 level in serotonin level from the 3^{rd} duration value to the 14^{th} day's groups as compared to control one.

Acetylcholinesterase activity recorded in the frontal hippocampus the data showed significant increase from the 3^{rd} day in ciprofloxacin and gatifloxacin administered groups as compared to control level till the 14^{th} day in cortex showed dose response significant increase ($P<0.05$) in AchE activity from the 3^{rd} ciprofloxacin or gatifloxacin dose administered achieving the maximum activity in the 14^{th} doses of both treatments as compared

Table 1. Effect of ciprofloxacin or gatifloxacin administration on amino acid neurotransmitters contents in rat frontal cortex and hippocampus.

Item	Group	Frontal cortex			Hippocampus		
		Experimental duration (days)					
		3	7	14	3	7	14
Glutamic acid	C	9.02±0.25	9.02±0.62	9.02±0.62	9.84±0.75	9.83±0.75	9.83±0.75
	Cip	6.44±0.19*	6.64±0.31*	8.35±0.66*^{ab}	9.86±0.620	8.65±0.15*^{a}	8.22±0.63*^{ab}
	Gati	6.33±0.15*	5.25±0.10*^{a}	6.09±0.25*^{b}	10.80±0.59*	10.26±0.48	12.30±0.22*^{ab}
Aspartic acid	C	2.18±0.10	2.18±0.10	2.18±0.10	1.93±0.13	1.93±0.13	1.93±0.13
	Cip	3.15±0.23*	2.89±0.15*^{a}	3.55±0.31*^{ab}	1.76±0.09*	1.23±0.07*^{a}	1.97±0.04^{ab}
	Gati	1.86±0.08*	2.43±0.11*^{a}	2.89±0.16*^{ab}	1.81±0.13*	2.10± 0.11*^{a}	2.13±0.05*^{a}
Asparagine	C	0.43±0.03	0.43±0.03	0.43±0.03	0.18±0.01	0.18±0.01	0.18±0.01
	Cip	0.52±0.04*	0.51±0.04*	0.76±0.06*^{ab}	0.25±0.01*	0.29±0.02*^{a}	0.21±0.01*^{ab}
	Gati	0.42± 0.02	0.53±0.03*^{a}	0.55±0.04*^{a}	0.29±0.02*	0.21±0.01*^{a}	0.33±0.01*^{ab}
Serine	C	0.47±0.04	0.47±0.04	0.47±0.04	0.23±0.02	0.23±0.02	0.23±0.02
	Cip	0.49±0.04	0.45± 0.04^{a}	0.55±0.04*^{ab}	0.21±0.02	0.20±0.01*	0.32± 0.01*^{ab}
	Gati	0.38±0.02*	0.56±0.03*^{a}	0.74±0.04*^{ab}	0.20±0.01*	0.21±0.02*	0.21± 0.01*
GABA	Cip	2.47±0.11	2.47±0.11	2.47±0.11	1.92±0.17	1.92±0.17	1.92±0.17
	Gati	1.58±0.10*	1.51±0.04*	1.70±0.15*^{ab}	2.79±0.24*	2.87±0.16*	2.52±0.08*^{ab}
		1.26±0.01*	1.38±0.06*^{a}	1.45±0.04*^{a}	2.94±0.15*	3.02±0.25*	3.02±0.09*
Glycine	C	1.71±0.15	1.71±0.15	1.71±0.15	0.99±0.06	0.99±0.06	0.99±0.06
	Cip	2.31±0.15*	2.13±0.08*^{a}	2.34±0.24*^{b}	1.32±0.05*	1.12±0.01*^{a}	1.70±0.14*^{ab}
	Gati	1.64±0.02	1.76±0.08	1.88±0.11*^{a}	1.33±0.01*	1.11±0.06*^{a}	1.05±0.04^{a}
Taurine	C	2.00±0.12	2.00±0.12	2.00±0.12	3.36±0.27	3.36±0.27	3.36±0.27
	Cip	1.98±0.14	1.78±0.07*^{a}	2.12±0.19^{ab}	3.59±0.22*	3.27±0.15^{a}	4.01±0.20*^{ab}
	Gati	1.95±0.02	1.99±0.05	1.58±0.06^{ab}	4.04±0.07	4.17±0.15	3.84±0.20^{b}

The results are presented as means ± standard deviation, n = 8 rats. *, significant change from the corresponding control value, ^{a}, significant change from the 3 days of treatment group, ^{b}, significant change from the 7days of treatment group at 0.05 level.C, control.

Table 2. Effect of ciprofloxacin or gatifloxacine administration on monoamine neurotransmitters contents and acetylcholinesterase enzyme activity in rat frontal cortex and hippocampus.

Item	Group	Frontal cortex			Hippocampus		
		Experimental durations (days)					
	(n=8)	3	7	14	3	7	14
Norepinepherine	C	1.06±0.01	1.06±0.01	1.06±0.01	0.56±0.13	0.56±0.13	0.56±0.13
	Cip	0.84±0.07*	0.92±0.08*^{a}	0.85±0.01*^{ab}	0.73±0.06*	0.982±0.09*^{a}	0.99±0.09*^{a}
	Gati	0.72±0.04*	0.72±0.06*	0.86±0.05*^{ab}	0.90±0.07*	0.77±0.05*^{a}	0.70±0.06*^{a}
Dopamine	C	3.36±0.23	3.36±0.23	3.36±0.23	0.66±0.11	0.66±0.11	0.66±0.11
	Cip	3.25±0.14	2.43±0.04*^{a}	1.71±0.09*^{ab}	1.60±0.14*	1.65±0.13*	0.92±0.04*^{ab}
	Gati	2.75±0.12*	2.74±0.23*	3.00±0.15*^{ab}	0.65±0.03	0.53±0.02*^{a}	0.61±0.04
Serotonin	C	85.40±7.71	85.40±7.71	85.40±7.71	244.80±18.36	244.80±18.36	244.80±18.36
	Cip	31.80±3.58*	54.90±5.62*^{a}	93.50±13.38*^{ab}	234.00±10.00	161.60±16.71*^{a}	223.70 ± 21.02*^{b}
	Gati	58.00±2.62*	49.60±4.21*^{a}	78.30±5.47*^{ab}	222.60±17.04*	208.50±5.40*	200.10±15.64*^{a}

Table 2. Contd.

	C	13.27±0.81	13.27±0.81	13.27±0.81	17.52±0.62	17.52±0.62	17.52±0.62
AChE	Cip	17.75±1.46*	23.39±1.07*[a]	32.30±2.30*[a]b	14.43±0.79*	13.48±0.85*	12.57±1.07*[a]
	Gati	16.02±2.23*	19.99±2.29*[a]	21.11±1.90*[a]	15.45±0.92*	14.70±0.71*	12.90±0.94*[ab]

The results are presented as means ± standard deviation, n = 8 rats. *, significant change from the corresponding control value, [a],' significant change from the 3 days of treatment group, [b], significant change from the 7days of treatment group at 0.05 level. C, control.

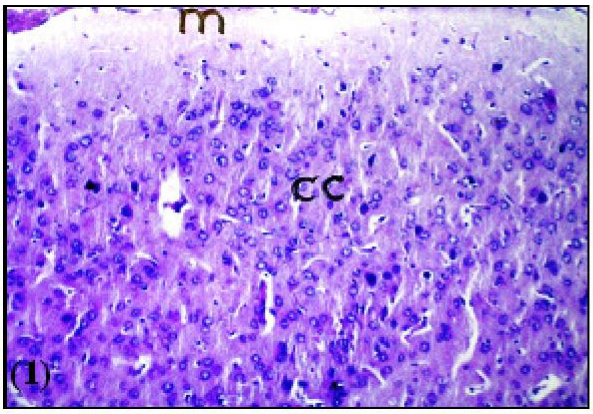

Figure 1. Normal histology of cerebral cortex (CC) and covering meninges (m) (H and E x-40).

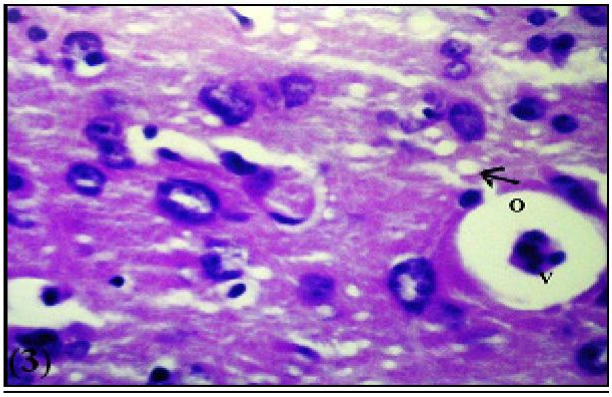

Figure 3. Three days cip showing vacuolation in the brain cerebral matix (arrow) associated with congestion of the blood vessels (v) and perivascular oedema (O). (H and E x-160).

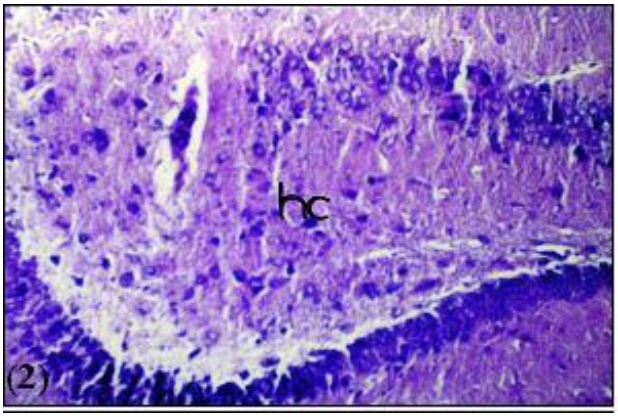

Figure 2. Normal rat histology of hippocampus (hc). (H and E x-40).

to the control enzyme activity. On the contrary, in the hippocampus, the data showed significant decrease in AchE activity from the 3rd till the 14th days of ciprofloxacin or gatifloxacin administration.

The hispopathological examination the response of cortex and hippocampus cells to ciprofloxacin and gatifloxacin administration at different durations is clearly investigated. The consequence damage to the cortical area of ciprofloxacin administered animals showed from the 3rd dose are vacuolation associated with congestion and perivascular oedema in the blood vessels and the meninges showed vascular congestion. Congestion with perivascular oedema in the blood vessels and capillaries of cerebral cortex achieved its severe stage at the final 14th day of ciprofloxacin administration. Also the cerebral matrix showed diffuse gliosis. Hippocampus of ciprofloxacin-administered animals showed from the 3rd dose congestion in the blood vessels attained the severe congestion with perivascular oedema in the blood vessels and capillaries of the hippocampus at the last examined duration of drug administration (Figures 1 to 8).

Gatifloxacin from the 3rd dose revealed moderate changes in the cerebral cortex in the form of neuronal degeneration, diffuse gliosis, and congestions with perivascular oedema in the blood vessels and capillaries with focal gliois at the end of the experiment. Hippocampus of gatifloxacin administered animals showed congestion in the blood vessels and capillaries, degeneration in the some hippocampal neurons after the3rd dose. The hippocampus showed vacuolation in the

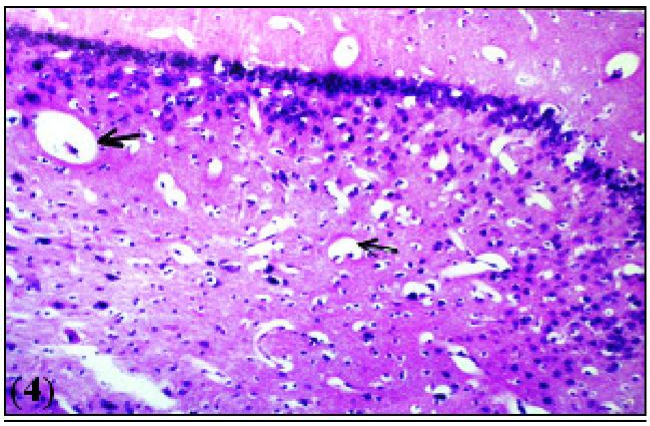

Figure 4. Three days cip showing congestion of blood vessels and capillaries (arrow) with perivascular oedema in the hippocampus. (H and E x-40).

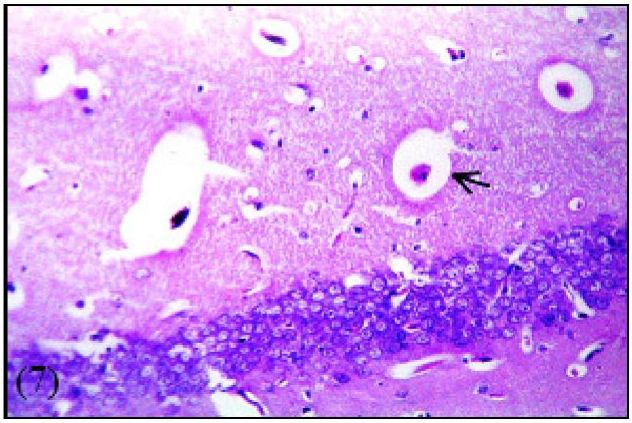

Figure 7. Fourteen days cip showing congestion of blood vessels with perivascular oedema in the hippocampus. (H and E x-40).

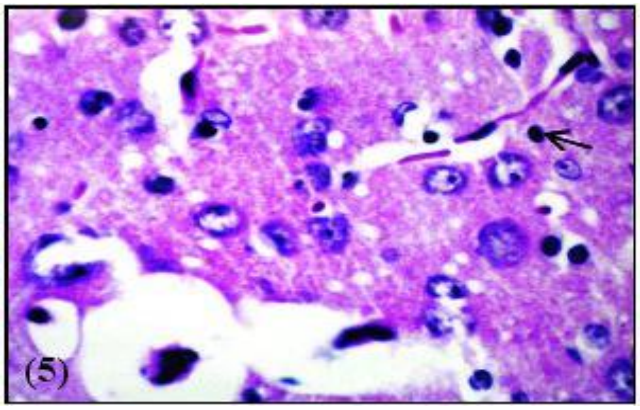

Figure 5. Seven days cip showing vacuolation of cerebral matrix (v), diffuse gliosis (arrow). (H and E x-40).

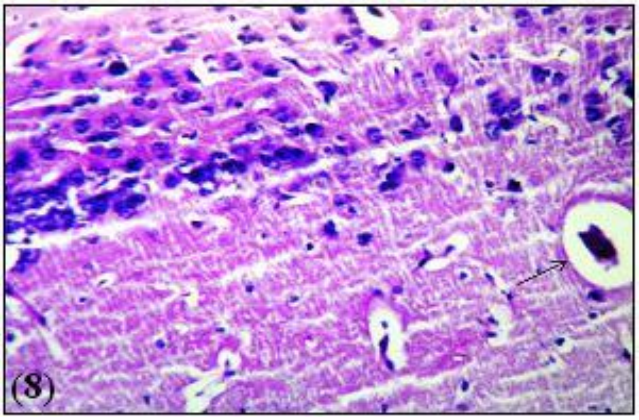

Figure 8. Fourteen days cip showing the magnification of figure (12) to identify the congestion and perivascular oedema of blood vessels in the hippocampus (arrow). (H and E x-160).

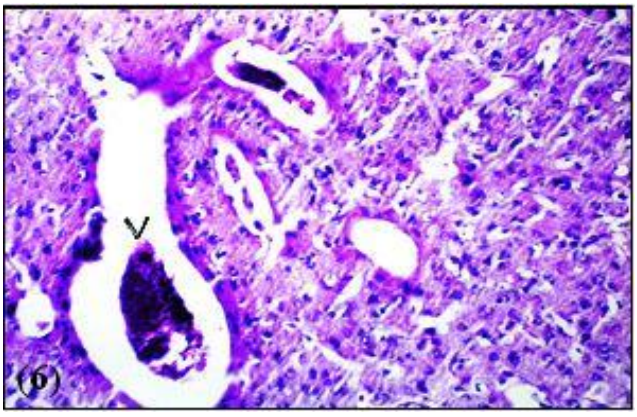

Figure 6. Fourteen days cip showing sever congestion of cerebral blood vessels with perivascular oedema. (H and E x-40).

tissue matrix with degeneration in the neuronal cells and congestion in the blood vessels and capillaries at the last dose group of gatifloxacin-administered rat (Figures 9 to 15).

DISCUSSION

In the present study the response of cortex and hippocampus areas to ciprofloxacin and gatifloxacin at different durations are clearly investigated through the determined amino acids and monoamines neuro-transmitters and the recorded activities of the acetylcholinesterase enzyme. The excitatory potencies of ciprofloxacin and gatifloxacin recorded throw the elevation

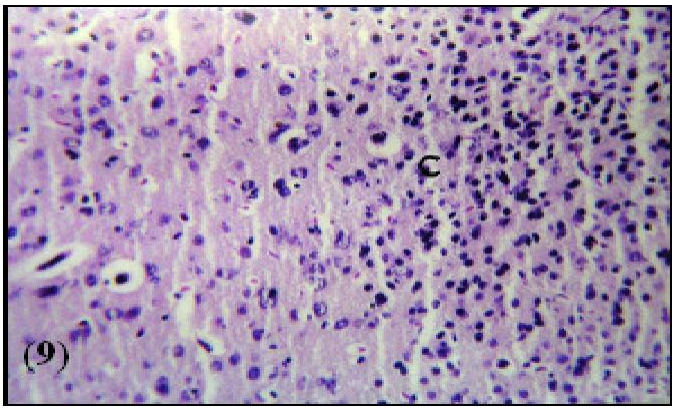

Figure 9. Three days gati showing diffuse gliosis in the cerebral matrix (C). (H and E x-64).

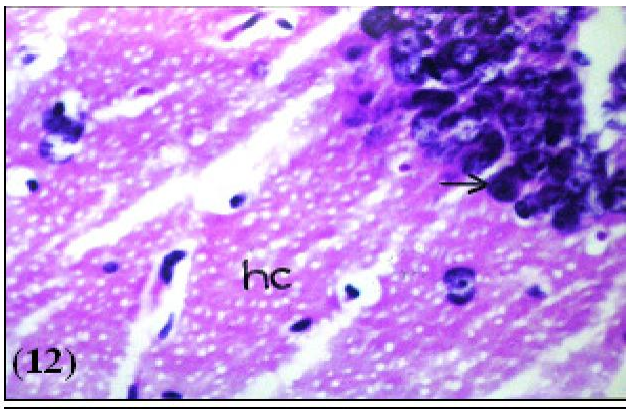

Figure 12. Seven days gati showing vacuolation in the hippocampus tissue matrix (hc) with degeneration in the neuronal cells (arrow). (H and E x- 160).

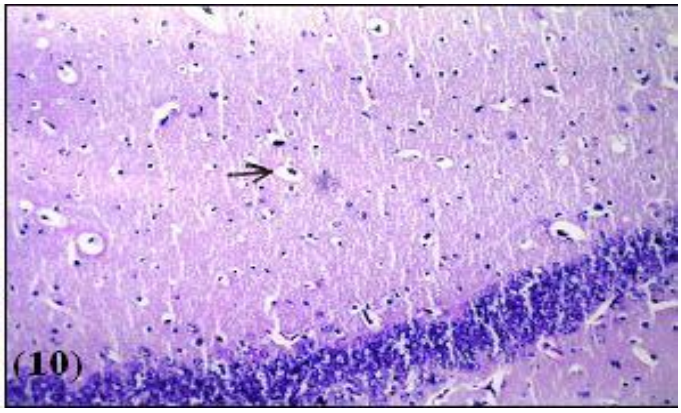

Figure 10. Three days gati showing congestion with perivascular oedema in the hippocampus blood vessels and capillaries (arrow). (H and E x-64).

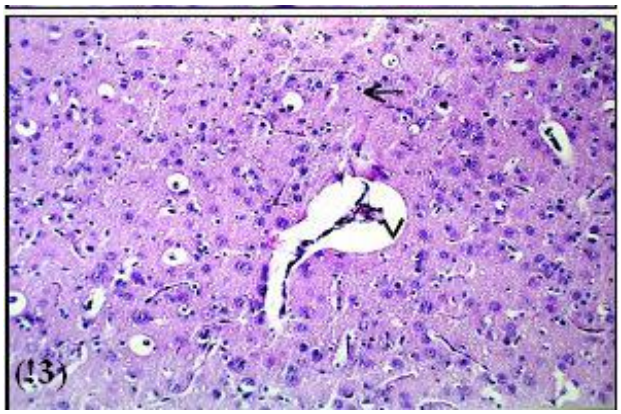

Figure 13. Fourteen days gati showing congestion of blood vessels and capillaries of the cerebral cortex with perivascular oedema (V) and diffuse gliosis (arrow). (H and E x- 64).

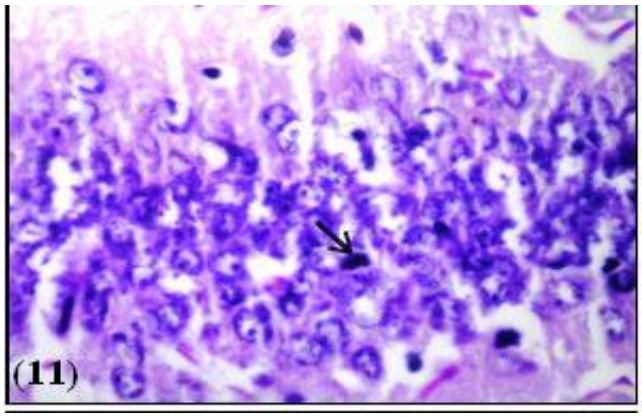

Figure 11. Three days gati showing degeneration of some neuronal cells in the hippocampus (arrow). (H and E x- 160).

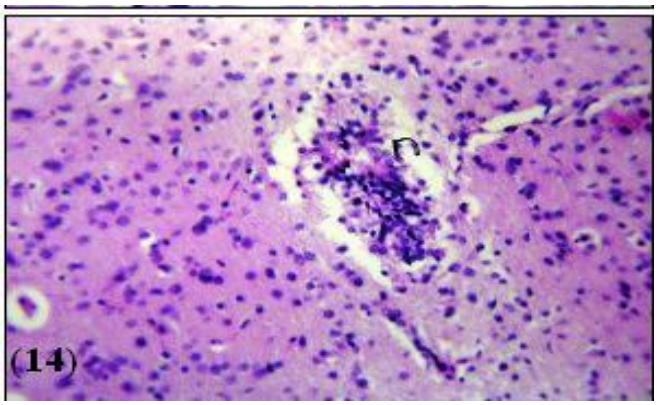

Figure 14. Fourteen days gati showing focal gliois (n) in the cerebral cortex. (H and E x- 64).

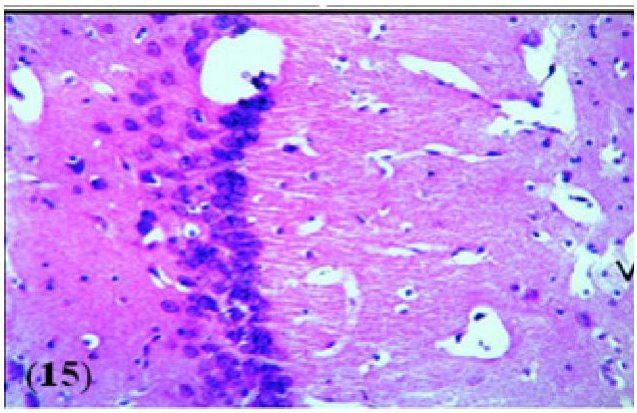

Figure 15. Fourteen days gati showing congestion in the blood vessels (V) in hippocampus. (H and E x- 160).

of aspartate and asparagine levels and the increase of the activities of AChE in spite of decrease of glutamate and monoamines levels in the cortical area as a result of either ciprofloxacin or gatifloxacin administrations in a time related effect. In addition, there was decrease of GABA and alanine levels in a manner as the aforementioned effect.

The excitatory potencies of the antibiotics under investigation varied as regard to the hippocampus area where ciprofloxacin in the hippocampus area recorded elevation of asparagines, GABA, glycine, taurine, norepinepherine and dopamine levels but decrease of glutamate and serotonin levels in a time related effect. In addition there are decreases of AChE activities and aspartate, glutamate levels in a dose related effect. But in case of gatifloxacin treated groups in the hippocampus area shows elevation of aspartate, glutamate, asparagines, GABA, glycine, taurine and Norepinepherine. Also there are decreases in the activities of AChE and the levels of dopamine and serotonin.

The previous findings, which recorded herein in brain cortical areas from groups subjected to the antibiotics, are in line with alterations in extrahippocampal regions in epileptic rat models as previous experimental findings have also demonstrated that the cortex damaged with diffuse gliosis in different animal models of acute limbic seizures. This alterations support the hyperexcitability with GABAergic inhibition, which could play a crucial role in seizure generation and expression in epileptic rat models (Silva et al., 2002).

The alterations in the hippocampus area evidence provided links early seizures with the later development of epilepsy and selective hippocampal neuronal loss (Koh et al., 1999). Also kindled seizures are associated with a selective degeneration of cortical and hippocampal areas (Szyndler et al., 2006) which supported by the elevation of GABA levels in hippocampus tissues of both antibiotics treated groups which in line with that recorded in kianic acid induced seizure rat animal model (Bruhn et al., 1992) and the assumption of Gale (1992) about the increase of GABAergic transmission can induce excitatory effects.

The anexiogenic effects due to ciprofloxacin and gatifloxacin may be supported through the recorded changes in the concentrations of frontal cortex amino acids. There were decreases in GABA and glutamate levels with a concomitant increase in aspartate, asparagine, glycine, serine and alanine contents which similar to those recorded in the frontal cortex of epileptic rat models (Craig and Hartman, 1973; Li et al*.,* 2000; Szyndler et al., 2006).

The regional differences in GABA level and acetylcholinesterase activity between decrease of GABA level and increase of AChE activity in the cortical area and increase of GABA level and decrease of AChE activity in the hippocampal area in both antibiotics treated groups in a dose related effect which mimics that predicted in rat epileptic models (Appleyard et al., 1986) and support the proconvulsant effect of the quinolones previously discussed (Smolders et al., 2002)

Experimental manipulations suggest that *in vivo* administration of cholinergic agonists or inhibitors of AChE increases the concentration of acetylcholine. Biochemical studies have proposed a role for AChE in brain mechanisms responsible by development to status epilepticus through decrease in the AChE activity in the hippocampus (Freitas et al., 2006)

It is evident from the present study that ciprofloxacin and gatifloxacin administered groups recorded significant decrease in the cortical main inhibitory amino acid GABA levels throughout the experimental periods in a dose related effect. GABA the principal inhibitory neurotransmitter in the cerebral cortex maintains the inhibitory tone that counterbalances neuronal excitation. When this balance is perturbed, seizures may ensue. GABA is formed within GABAergic axon terminals and released into the synapse, where it acts at one of two types of receptor: GABAA, which controls chloride entry into the cell, and GABAB, which increases potassium conductance, decreases calcium entry, and inhibits the presynaptic release of other transmitters. GABAA-receptor binding influences the early portion of the GABA-mediated inhibitory postsynaptic potential, whereas GABAB binding influences the late portion. GABA is rapidly removed by uptake into both glia and presynaptic nerve terminals and then catabolized by GABA transaminase. Experimental and clinical study evidence indicates that GABA has an important role in the mechanism of epilepsy as abnormalities of GABAergic function have been observed in genetic and

acquired animal models of epilepsy, reductions of GABA-mediated inhibition, activity of glutamate decarboxylase, binding to GABAA and benzodiazepine sites. GABA antagonists produce seizures and drugs that inhibit GABA synthesis cause seizures (Treiman, 2001).

Reduction in inhibitory control due to loss of GABAergic interneurons, and a decrease in GABA levels and GABAA receptor sensitivity leads to cortex hyperexcitability as GABAergic neurotransmission and epilepsy has long been recognized. Inhibition of GABAA receptors triggers acute seizures (Prince, 1978; Olsen and Avoli, 1997; Armijo et al., 2002).

The role of γ-aminobutyric acid (GABA) in anxiety is well documented (Davis et al., 1994) Some studies indicate that fluoroquinolones function as GABA receptor antagonists, (Unseld et al., 1990) and the epileptogenic action of quinolones has been proposed to be related to the GABA-like structure of ring substitutes. Quinolones have an inhibitory effect on the receptor binding of GABAA, and may thus exert an inhibitory CNS stimulant action (Akahane et al., 1994; Imanishi et al., 1995). Benzodiazepine agonists have been reported to attenuate the central stimulating effects of ciprofloxacin and pefloxacin (Unseld et al., 1990) Likewise, they potentiate chemically-induced convulsions, which could be antagonised by benzodiazepines. (Enginar and Eroğlu, 1991) The adenosine or GABAA receptor has therefore been proposed as a possible target for ciprofloxacin (Dodd et al., 1988).The structural similarities of the fluoroquinolones to kynurenic acid and other similar compounds, which are endogenous ligands of the glutamate receptor, might suggest an interaction of quinolones with ligand-gated glutamate receptors as well (Schmuck et al., 1998) which may explain the elevated hippocampual glutamate level in the gatifloxacin subjected groups.

The decreased glutamate level in the cortical area of either ciprofloxacin or gatifloxacin treated groups and the ciprofloxacin treated group hippocampus area, may be explained as fluoroquinolones did not bind to the glutamate or glycine-binding site of the *N*-methyl-D-aspartate (NMDA) receptor. It has been shown that fluoroquinolones decrease blocking effects of Mg2+ and MK-801 binding to the NMDA receptor. Magnesium chelating properties of fluoroquinolones have been postulated as mechanisms of fluoroquinolone-induced atrophy, and the excitatory potency of fluoroquinolones might also be based on activation of the NMDA receptor by abolishing the Mg2+ block in the ion channel. This would prolong the opening time of the channel, thus increasing intracellular Ca2+ concentration in the neurons (Sen et al., 2007).

The decrease of glutamate and increase of aspartate may be explained through the glucose homeostasis abnormalities (dysglycemia) associated with the use of gatifloxacin (Onyenwenyi et al., 2008) as aspartate seems to selectively activate the NMDA type of Glutamate receptors (Curras and Dingledine, 1992). Electrophysiological experiments using hippocampal slices have demonstrated that when glucose concentration was reduced, stimulation of the Schaffer collaterals gave an Aspartic-mediated NMDA response (Fleck et al., 1993), indicating a functional role of Asp released from excitatory nerve endings. Immunocytochemistry has detected NMDA receptors in target neuronal cell bodies and dendritic spines contacted by the type of nerve endings shown here to be enriched with Asp during hypoglycemia (Takumi et al., 1999). In hippocampal neurons, a larger number of quanta transmitters are signaled through NMDA receptors than through alpha amino 3-hydroxy 5-methyl 4-isoxazoleproprionic acid receptors, and during repetitive neuronal firing some of the released transmitter can spill over from the synaptic cleft to activate extrasynaptic NMDA receptors (Kullmann et al., 1996). Thus, leakage of aspartate not only from excitatory but also from inhibitory synapses during conditions of high neuronal activity, in which the release of aspartate is, enhanced (Szerb, 1988), may reach NMDA receptors at nearby sites and cause an enhanced NMDA receptor response during these conditions. Thus, aspartate could play an important role in physiologic and pathologic types of NMDA receptor-mediated transmission. Could such an aspartate-induced NMDA receptor response be involved in hypoglycemic neuronal death? Neurons susceptible to hypoglycemia comprise dentate granule cells, pyramidal cells in CA1 of hippocampus, and striatal neurons (Auer et al., 1984).

During hypoglycemia, the excitatory and inhibitory nerve terminals contacting these neurons are enriched with Aspartate, which may be released to activate NMDA receptors on synaptic and extrasynaptic sites. This would cause an excitotoxic insult, leading to neuronal death (Wieloch, 1985). In line with this is the recent demonstration in hippocampal neurons that excitotoxicity was not only caused by activation of NMDA receptors at the postsynaptic density but also by activation of NMDA receptors at extrasynaptic sites (Sattler et al., 2000).

The elevated level of glycine in cortical and hippocampus areas of rats subjected to ciprofloxacin or gatifloxacin may be declared the effect of the inhibitory neurotransmitter glycine on slow destructive processes in brain cortex slices under anoxic conditions as glycine, the simplest of the amino acids, is an essential component of important biological molecules, a key substance in many metabolic reactions, the major inhibitory neurotransmitter in the spinal cord and brain stem, and an anti-inflammatory, cytoprotective (Gundersen et al., 2005; Tonshin et al., 2007). In hippocampus area the experi-mental model of epilepsy during kianic acid induced

epilepsy the results indicated that the levels of glutamate, aspartate, glycine and GABA were statistically increased in rat's hippocampus (Liu and Cheng, 1995) which is in line with our hippocampal results in ciprofloxacin or gatifloxacin treated groups supporting body of studies about proconvulsant and anxiogenic effects of ciprofloxacin and gatifloxacin (Quigley and Lederman, 2004; Bharai et al., 2008) and epileptogenic potential (Koussa et al., 2007) which extended to that long term administration of gatifloxacin for 14 days was found to indicate movement impairing effect in mice (Bharai et al., 2008).

Metabolic actions of taurine include: bile acid conjugation, detoxification, membrane stabilization, osmoregulation, and modulation of cellular calcium levels. Clinically, taurine has been used with varying degrees of success in the treatment of a wide variety of conditions, including: cardiovascular diseases, hypercholesterolemia, epilepsy and other seizure disorders, macular degeneration, Alzheimer's disease (Birdsall, 1998).

About the taurine detected levels which increased and these may be related to the extracellular increased levels of excitatory amino acids which led to neuronal, glial and endothelial impairment through the NMDA receptors activation and the increase of the intracellular Ca^{2+} concentration which is a signal for taurine release, which in turn blocks NMDA-evoked Ca^{2+} entry. This increase in the extracellular taurine level serves a neuromodulator that protects against cell damage from the Ca^{2+} influx which followed by Cl^{-} influx resulting in cell swelling and eventually cell death (Yang et al., 1997). Hence taurine, a volume regulating amino acid, increased inducing cell swelling as predicted through the level of taurine measured or the histopathological examination and this is in agreement with Stover et al. (1997). The increased taurine levels in the hippocampus may involve processes for membrane stabilization, thus favoring recovery after neuronal hyperactivity. In the hippocampus of epileptic patients found increases in taurine, glutamate, aspartate during seizures (Wilson et al., 1996) also it was reported that the intraperitoneal injection of taurine blocked the convulsive seizure in rat cortex (Batuev et al., 1997).

Thus the herein recorded increase in taurine levels could be explained as involvement in the modulation of spontaneous recurrent seizure activity (Baran, 2006).

It has been suggested that the biogenic amines such as Norepinepherine, dopamine and serotonin play important role in the manifestation and inhibition of convulsions since several animal models of convulsion may be significantly affected by modifying the levels or availabilities of these amines in the brain.

The effect of brain amines on convulsion has been demonstrated to differ depending on the method of seizure induction. However, there are virtually no detailed studies investigating the relationship between the type of stimulation used for convulsion induction and the effects on brain amines. The main reason is due to the differences of neurons participated in the response to the given stimuli to elicit the convulsions. For example the electrical stimulation none selectively stimulates almost all kinds of neurons with different neurotransmitters while the chemical stimulation can distinguish the specialized receptor to make an excitation in the brain so monoamines in the hippocampal seizure discharge are very much dependant on the type of stimulation employed (Nishi et al., 1981; Meldrum, 1991). It was found in the kindling model of epilepsy, for instance, Norepinepherine and serotonin depletion have been shown to facilitate development of seizures in rats (Corcoran and Mason, 1980; Cavalheiro et al., 1981; Bortolotto and Cavalheiro, 1986), and increased Norepinepherine concentration in hippocampus of rats subjected to kindling has been demonstrated by microdialysis (Kokaia et al., 1989). The levels of biogenic amines such as dopamine, serotonin and nor-adrenaline in the forebrain region seizures induced by Maximal Electro shock (MES) method in rats (Balamurugan et al., 2009). Bidziński et al. (1998) concluded that there is a functional interaction between brain serotonin and GABA systems, both at behavioral and biochemical levels, that is involved in the motor activity habituation process due to the effect of serotonin depletion in GABAA receptor down-regulation.

Monoamines levels recorded in the tested antibiotics shows reduction in norepinepherine, dopamine and serotonin in the frontal cortex in the ciprofloxacin and gatifloxacin treated groups. But in hippocampus there are elevations in Norepinepherine and dopamine and reduction of serotonin levels in ciprofloxacin subjected groups. On the other hand there is elevation of norepinepherine and reduction of dopamine levels in the gatifloxacin treated groups. These data may be validated the seizure induction through the assumption about the pharmacological treatments that lowering monoamine levels in the brain generally increase the susceptibility to seizures, while treatments that increase monoamines decrease the susceptibility (Kiyofumi and Akitane, 1977). The data recorded about monoamines in the tested antibiotics may be a supplement data to the previously mentioned seizure inducing activity of quinolones (Ooie et al., 1997; Moorthy et al., 2008; Agbaht et al., 2009).

Overall, these data suggest that there is a shift in the balance between neurotransmitters towards increased production of excitatory amino acids, and this may be triggering seizure in rat model (Szyndler et al., 2008). The excitatory potency reported effect of quinolones evaluated through the elevation of aspartic acid, asparagine and norepinepherine in addition to the reduction of the GABA level and in the frontal cortex and

reduction of the GABA level and in the frontal cortex and elevation of Norepinepherine contents in hippocampus tissue in groups subjected to ciprofloxacin. Also the recorded AChE enzyme activity reduced in hippocampus gatifloxacin administration excitatory potency recorded through elevation of frontal cortex Norepinepherine and glutamic acid and Norepinepherine levels in hippocampus tissues. Also the recorded AChE enzyme activity reduced in hippocampus.

Therefore, the design and development of new quinolone derivatives with broader antibacterial activity and better pharmaco-kinetics avoiding CNS side effects are attractive therapeutic goals. In addition, although further studies are needed to investigate the mechanism that causes the CNS side effects of quinolones, physicians should consider the possible epileptogenic activity of these compounds when treating patients with predisposing epileptic factors or when the penetration of quinolones into the brain via a damaged blood-brain barrier is enhanced. Thus dosing modifications and awareness of possible central nervous system adverse effects are warranted.

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