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Vol. 9(4), pp. 65-73, 29 January, 2015
DOI: 10.5897/AJPP2014. 4231
Article Number: 4BCF40A50432
ISSN 1996-0816

http://www.academicjournals.org/AJPP

African Journal of Pharmacy and Pharmacology

Full Length Research Paper

Exploration of the neurotoxicity of ciprofloxcin or gatifloxacin single dose in rat cortex and hippocampus

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Received 15 November, 2014; Accepted 29 January, 2015

The study aimed to evaluate the neurotoxicity of ciprofloxacin (Cip) or gatifloxacin (Gati) single oral dose in male albino rats weighing (100 ± 20 g) grouped as control-administered water, ciprofloxacin (80 mg/kg) and gatifloxacin (32 mg/kg) each of 12 rats. The frontal cortex of both groups revealed decrease in glutamate, GABA, taurine, histidine and serotonin levels and elevation of aspartate, glycin and serine and AChE activities. While noradrenaline and dopamine levels reduced significantly in Gati group, noradrenaline increased significantly in Cip group. Hippocampus of either Cip or Gati group's results revealed elevation of all detected amino acids and monoamines except the reduction of glutamate, aspartate and dopamine in Cip group. In the meantime, AChE activities significantly reduced in both treatments. Serum results showed elevation of glucose in both treated groups. The histological examination of Gati brain tissue showed neuronal degeneration in the cerebral cortex and congestion in the blood vessels and capillaries in hippocampus tissue without histopathological alteration observed in Cip group tissue. Overall, the data showed the effect of the quinolones single dose towards hyperglycemia and shift in balance of neurotransmitters and acetylcholinesterase as well as the histopathological alterations in the tested brain areas.

Key words: Ciprofloxacin, gatifloxacin, cortex, hippocampus, neurotransmitters, glucose.

INTRODUCTION

Gatifloxacin is one of the broad-spectrum fluoroquinolones available and approved by the US food and drug administration (FDA) in December 1999. Ever since its release in the market, there have been numerous reports implicating gatifloxacin as a cause of hypoglycemia and hyperglycemia. 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

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al., 2007). Gatifloxacin showed to be equivalent to ciprofloxacin for the treatment of acute uncomplicated lower urinary tract infections (Naber et al., 2004). In extensive *in vivo* and *in vitro* experiments performed in an attempt to explain the central nervous system (CNS) side effects of quinolones sometimes observed under therapeutic conditions, they are 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 were 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).

Seizure activity is associated with a wide range of local biochemical changes, affecting various neurotransmitters (monoamines, amino acids) (Freitas et al., 2004; Cavalheiro et al., 2006). 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) and suggested playing a role in inducing convulsions by quinolones (Motomura et al., 1991). The US Food and Drug Administration (FDA) Safety Announcement (8-15-2013) has recently issued a warning about fluoroquinolone antibacterial drugs; serious side effect of peripheral neuropathy may occur soon after these drugs are taken and may be permanent.

The study designed using single oral dose of the tested quinolones to explore its neurotoxicicity as the single dose in accordance with previous studies where it was used for treatment (Loo et al., 1985), randomized controlled trials (Boy et al., 2004; Kaushik et al., 2010; Heidari Bateni et al., 2014) and its prophylactic activity (Terzi et al., 2005; Alborzi et al., 2008). The study aims to ascertain the effect of oral single dose of either Cip or Gati in male albino rat on the concentrations of amino acid and monoamine neurotransmitters and acetylecholinesterase activities in the frontal cortex and hippocampus brain areas and the histopathological examination of both areas, in addition to the determination of serum glucose level.

MATERIALS AND METHODS

Experimental animals

This study carried was out on thirty-six adult male albino rats (*Rattus norvegicus*) with average body weight of range 100 ± 20 g obtained from the Egyptian Institution of Serum and Vaccine (Helwan). The experiment was 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 period. The experimental animals were allowed acclimating 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 water *ad libitum*.

Drugs

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 and 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) was administered 2 ml of distilled water, the second group (Cip) was administered 80 mg/100 g body weight ciprofloxacin dissolved in 2 ml water. The Gati-treated rat groups (n = 48 rats) was administered 32 mg/100 g body weight gatifloxacin dissolved in 2 ml water. Animals were sacrificed after 12 h from dose administration by rapid decapitation. Blood samples were collected and sera separated for assessment of glucose using the BioAssay Systems' glucose assay kit (QuantiChromTM Glucose Assay Kit). The brains were dissected out quickly, weighed and cleaned. Four brains from each treated group were served for the histopathological examination according to Banchroft et al. (1996) and the rest eight brains for the biochemical analysis. The frontal cortex and hippocampus areas were separated and divided into two halves; the first half was served for acetylcholinesterase activity assay according to the modification of Ellman et al. (1961) method as described by Gorun et al. (1978). 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. 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).

Statistical analysis

Reported values were represented as means ± SE. Statistical analysis was evaluated by one-way ANOVA. Once a significant F-test was obtained, least significance difference (LSD) comparisons was performed to assess the significance of differences among various groups using statistical processor system support "SPSS" for Windows software, Release 20.0 (SPSS, Chicago, IL).

RESULTS

The data as presented in Figure 1 as percentage change from control about frontal cortex showed decrease in

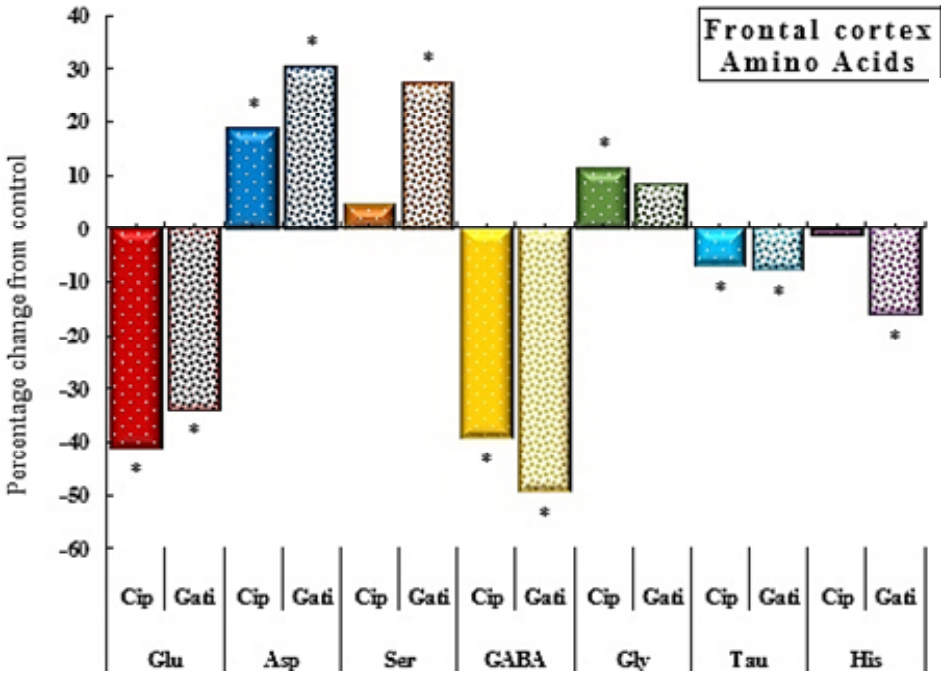

Figure 1. Percentage change from control of amino acids in cortices of rats treated with either ciprofloxacin (Cip) (80 mg/kg) or gatifloxacin (Gati) (32 mg/kg) single dose.

levels of glutamic acid, GABA, taurine and histidine and increase in aspartic, glycine and serine levels post administration of either ciprofloxacin or gatifloxacin. In ciprofloxacin group, glutamic acid, GABA, taurine and histidine data as mean ± SE is given as 5.32 ± 0.17 (-40.97%), 1.51 ± 0.05 (-39.02%), 1.86 ± 0.04 (-6.85%) and 1.20 ± 0.01 (-1.15%), respectively, while in gatifloxacin group, results are given as 5.99 ± 0.15 (-33.60%), 1.26 ± 0.003 (-49.21%), 1.85 ± 0.06 (-7.45%) and 1.03 ± 0.02 (-15.76%) different from control values 9.02 ± 0.25, 2.47 ± 0.04, 2.00 ± 0.05 and 1.22 ± 0.03, respectively. Aspartic acid increased significantly after ciprofloxacin and gatifloxacin: 3.37 ± 0.06 (18.49%) and 2.84 ± 0.06 (30.10%), respectively, from control value 2.18 ± 0.04. Serine level increased significantly after gatifloxacin: 0.60 ± 0.02 (27.23%) and not statistically different after ciprofloxacin administration: 0.49 ± 0.01 (4.47%), respectively, from control value 2.18 ± 0.04. Glycine level increased significantly after ciprofloxacin: 1.90 ± 0.04 (10.97%) and not statistically different after gatifloxacin administration 1.85 ± 0.06 (8.05%) from control value 1.71 ± 0.06.

The data represented in Figure 2 as percentage change from control about hippocampus showed no statistically different decrease in glutamic acid level and significant decrease in level of aspartic acid in ciprofloxacin group recording 9.17 ± 0.20 (-6.72%) and 1.53 ± 0.06 (-20.67%), respectively from control values 9.83 ± 0.30, 1.93 ± 0.05, respectively. Meanwhile, serine, GABA, glycine and histidine levels increased significantly in ciprofloxacin group recording values, 0.25 ± 0.005 (11.89%), 2.46 ± 0.08 (27.67%), 1.14 ± 0.01 (13.91%) and 2.70 ± 0.09 (9.65%), respectively from control values 0.23 ± 0.01, 1.92 ± 0.07, 1.00 ± 0.02 and 2.47 ± 0.07, respectively. Amino acids level in hippocampus of gatifloxacin group showed no statistically different increase in glutamic acid recording: 10.39 ± 0.26 (5.60%). Meanwhile, it showed significant increase in all detected amino acids recording values as: 1.98 ± 0.03 (2.37%), 0.28 ± 0.01 (22.03%), 3.17 ± 0.10 (64.59%), 1.44 ± 0.05 (44.04%), 3.62 ± 0.07 (7.75%) and 2.71 ± 0.06 (10.02%) for aspartic, serine, GABA, glycine, taurine and histidine, respectively.

Monoamines level and acetylcholinesterase activities recorded percentage change from control in frontal cortex and hippocampus of treated groups as well as serum glucose presented in Figure 3. In ciprofloxacin group, noradrenaline increased significantly in frontal cortex and hippocampus as mean ± SE by 1.19 ± 0.03 (12.44%) and 0.65 ± 0.03 (15.60), respectively. While in gatifloxacin group, noradrenaline decreased significantly in frontal cortex recording 0.78 ± 0.03 (-26.48%) and significantly

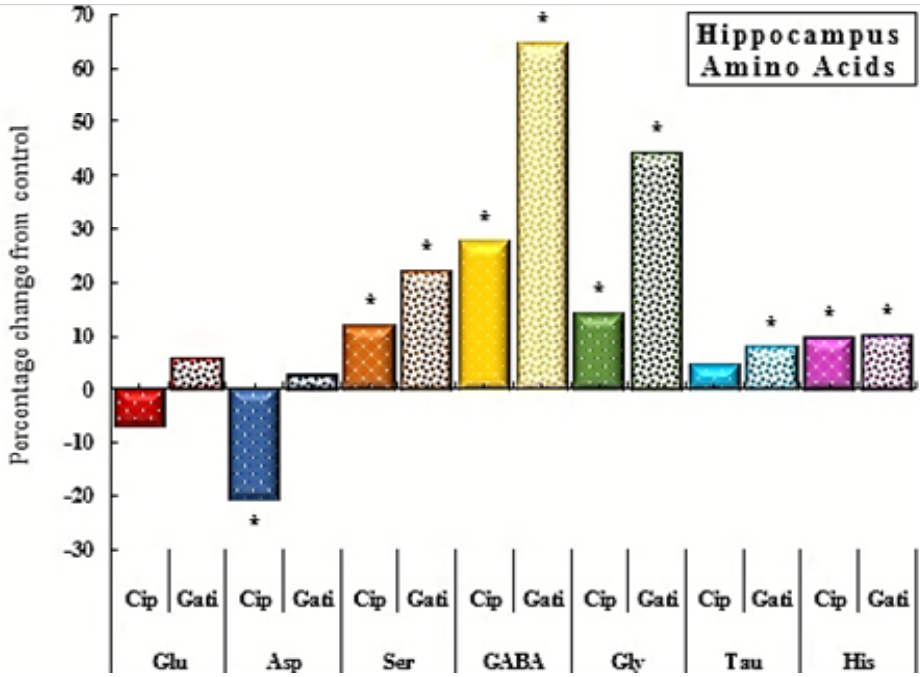

Figure 2. Percentage change from control of amino acids in hippocampi of rats treated with either ciprofloxacin (Cip) (80 mg/kg) or gatifloxacin (Gati) (32 mg/kg) single dose.

increased in hippocampus 0.87 ± 0.01 (54.79) from control values 1.06 ± 0.004 and 0.56 ± 0.05, respectively. Dopamine decreased significantly in frontal cortex of gatifloxacin group 2.95 ± 0.05 (12.21%) from control value 3.36 ± 0.11. Serotonin level decreased significantly in cortical area of ciprofloxacin and gatifloxacin groups 0.07 ± 0.001 (-15.30%) and 0.48 ± 0.002 (-43.53%), respectively from control value 0.08 ± 0.003. Meanwhile it increased significantly in hippocampus of gatifloxacin group 0.29 ± 0.004 (19.95%) from control value 0.25 ± 0.006.

Acetylcholinesterase activities increased significantly in frontal cortex while it decreased significantly in hippocampus of both treatments recording in frontal cortex activities of 16.7 ± 0.61 (21.82%) and 15.64 ± 0.91 (17.84%) in ciprofloxacin and gatifloxacin groups, respectively from control value 13.27 ± 0.33. While in hippocampus the data recorded was 15.47 ± 0.55 (-11.70%) and 16.23 ± 0.61 (-7.36%) in ciprofloxacin and gatifloxacin groups, respectively from control value 17.52 ± 0.25. In addition, serum glucose level increased, recording 16.7 ± 0.61 (21.82%) and 121.88 ± 3.50 (40.69%) in ciprofloxacin and gatifloxacin groups, respectively from control value 86.63 ± 0.93. With regards to the hispopathological examination, the response of cortex and hippocampus cells to Cip and Gati administration is represented in Figure 4A to D. Figure 4A and B showed normal histology of cerebral cortex and hippocampus in control group. There was no histopathological alteration observed in hippocampus of Cip group in Figure 4C, while in Gati group there was neuronal degeneration in the cerebral cortex (Figure 4D) associated with congestion in the blood vessels and capillaries of the hippocampus (Figure 4E).

DISCUSSION

Fluoroquinolones had structural similarities to kynurenic acid and other similar compounds which are endogenous ligands of the glutamate receptor, which might suggest an interaction of quinolones with ligand-gated glutamate receptors as well (Schmuck et al., 1998), and may explain the effect on quinolones subjected groups. The excitatory potency of fluoroquinolones is based on activation of the N-Methyl-d-aspartate (NMDA) receptor by abolishing the Mg^{2+} block in the ion channel which would prolong the opening time of the channel, thus increasing intracellular Ca^{2+} concentration in the neurons (Sen et al., 2007). The characteristics of gatifloxacin transport across blood brain barrier were investigated using primary cultured rat brain microvessel endothelial cells (rBMECs) as an *in vitro* model and study suggested that gatifloxacin transport across rBMECs involves a

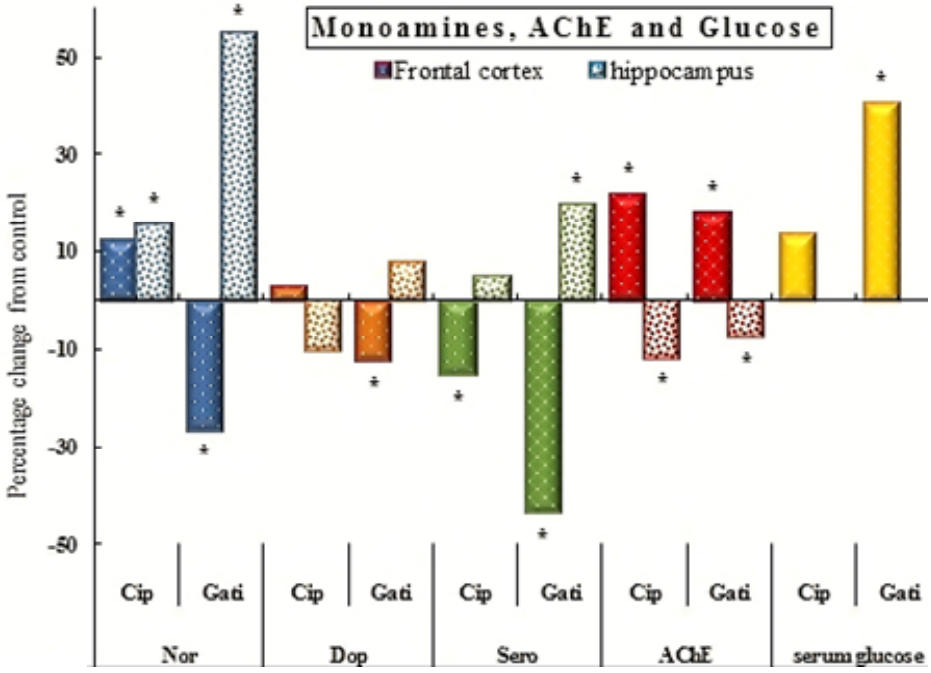

Figure 3. Percentage change from control of monoamines and acetylcholinesterase (AChE) in cortices and hippocampi and serum glucose of rats treated with either ciprofloxacin (Cip) (80 mg/kg) or gatifloxacin (Gati) (32 mg/kg) single dose.

$Na+/Ca^{2+}$ exchange mechanism and extracellular Ca^{2+} (Li et al., 2009). The effect on Ca^{2+} may declare the effect of both antibiotics on taurine levels detected favoring recovery after neuronal hyperactivity (Rawi et al., 2011). Elevated aspartate, serine and glycine might suggest to the excitatory potencies of fluoroquinolones through their activation role on N-Methyl-D-aspartate-type glutamate receptor (NMDAR) (Curras and Dingledine, 1992; Wolosker, 2006; Wolosker et al., 2008).

The regional differences in GABA levels and acetyl-cholinesterase activities recorded decrease of GABA level and increase of AChE activity in the cortical area. Meanwhile, increase of GABA level and decrease of AChE activity in the hippocampal area in both treatments 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; Abdel-Rahman et al., 2013; Arafa et al., 2013). Biochemical studies proposed role for AChE in brain mechanisms in development of status epilepticus through decrease in the AChE activity in the hippo-campus (Freitas et al., 2006). The effect of ciprofloxacin and gatifloxacin on GABA levels and acetyl-echolinesterase activities in cortex and hippocampus and their relation to anixiety and seizure generation was discussed in our previous study (Rawi et al., 2011; Abdel-Rahman et al., 2013). Seizure induction or decrease seizure threshold related effect to either ciprofloxacin or gatifloxacin single dose was previously declared (Darwish, 2008; Quigley and Lederman, 2004). In addition, serine elevation might be related to hippocampal serotonin increment detected in our study (Santini et al., 2014). Histidine content decreased in the frontal cortex and increased in hippocampus of ciprofloxacin and gatifloxacin treated groups. Histamine synthesis rate is a function of histidine content and histidine raises the possibility of a profound direct effect on CNS function (Yoshimatsu et al., 2002) and the herein results support the anaphylactoid reactions and hypotensive action of quinolones under therapeutic conditions as reported by Furuhata et al. (1998), Johannes et al. (2007) and Jones et al. (2013).

Fluoroquinolone-associated anaphylaxis may occur after first-ever intake of the agent (Sachs et al., 2006). In addition, drugs that release histamine may provoke headache, asthma, hypotension, arrhythmia, urticaria, pruritus, flushing and other conditions in patients with histamine intolerance (Maintz and Novak, 2007). Monoamines levels recorded in the tested antibiotics shows elevation in noradrenaline and reduction in dopamine and serotonin in the frontal cortex in the Cip and Gati groups except reduced level of noradrenalin in Gati group. However, in hippocampus there are elevations in monoamines levels in both groups except reduction of dopamine level in Gati group. These data

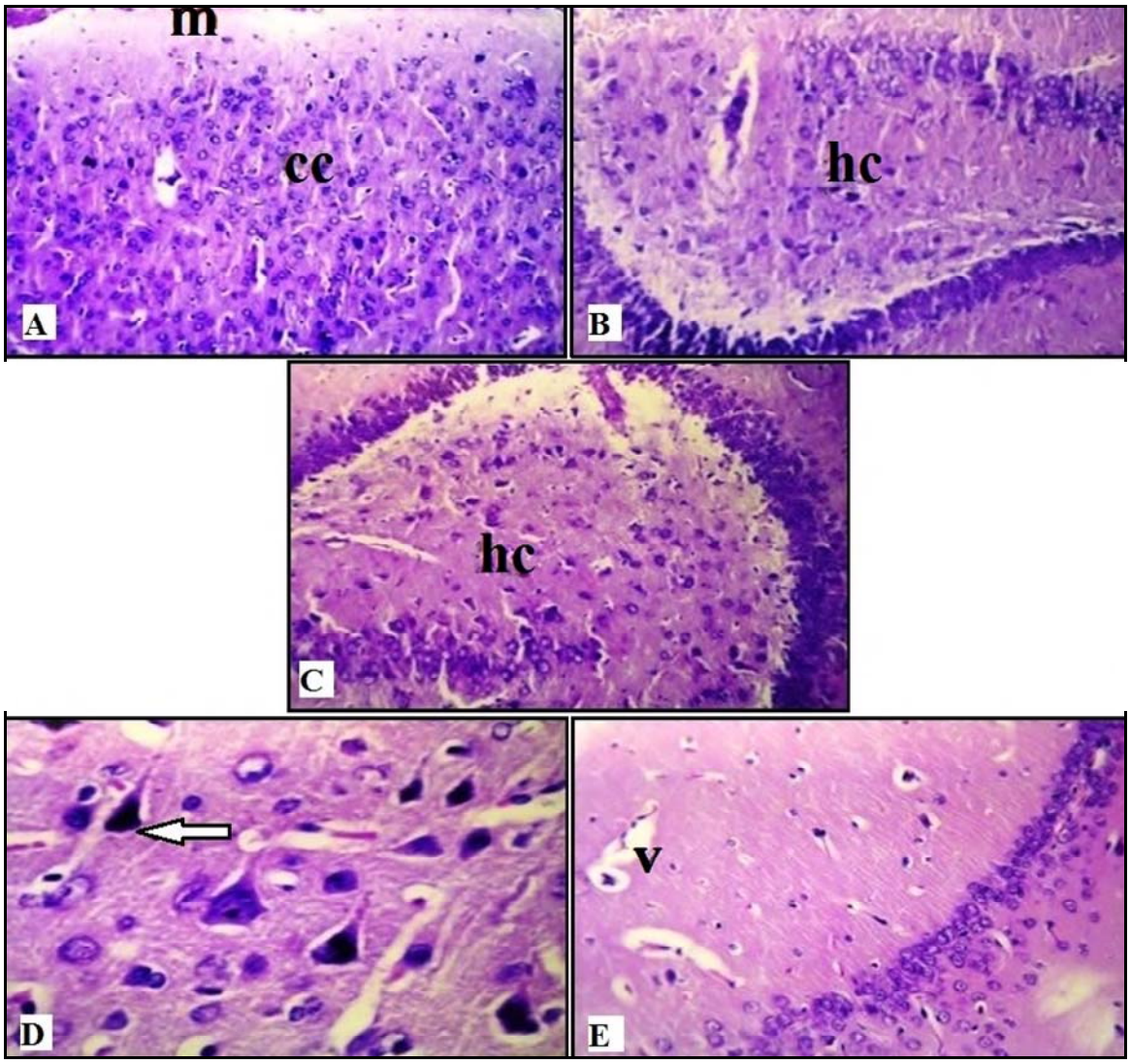

Figure 4. Light micrographs of brain sections in treated groups showing in control group normal histology of cerebral cortex (CC) and covering meninges (m) (H&E × 40) (A) and normal rat histology of hippocampus (hc). (H&E × 40) (B). Normal histological structure observed in the hippocampus tissue (hc) in ciprofloxacin group. (H&E × 40) (C). Neuronal degeneration in the cerebral cortex (arrow). (H&E × 160) (D), and congestion in the blood vessels and capillaries of the hippocampus (H&E × 64) (E) in gatifloxacin group.

may be validated by 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). The involvement of prefrontal cortex in depression and the link between reduced serotonin level in prefrontal cortex and depression symptoms as previously stated (Juckel et al., 1999; Koenigs and Grafman, 2009) is in accordance with the levels detected in our study. So the increment in the intracellular Ca^{2+} ions led to the rupture of the vesicles in the presynaptic terminals and increased the release of the neurotransmitters (Bullock et al., 1995) as a result, the content of catecholamine is decreased. The neuro-transmitters alterations support the hyperexcitability which reflected on the histopathology of cortex and hippocampus mainly in the most affected Gati group in

line with several previous studies discussed in Rawi et al. (2011) and Arafa et al. (2013).

As regard to the effect on glucose level in tested groups, Yamada et al. (2006) reported the effect of gatifloxacin on insulin secretion and islet insulin content by using isolated mouse pancreatic islets. Islet insulin content significantly decreased by gatifloxacin already at day one; however, there are some case reports that show that only one or two doses of gatifloxacin can induce hyperglycemia (Biggs, 2003; Arce et al., 2004). Gatifloxacin was withdrawn from clinical use after reports of drug-induced hyperglycemia and other fluoroquinolones reported to interfere with glucose homeostasis (Telfer, 2014). Onyenwenyi et al. (2008) indicated that non-diabetic gatifloxacin treated patients appeared to have an increased risk of hyperglycemia and the risk reduced in diabetics. Ghaly et al. (2009) previously documented that fluoroquinolones did not stimulate insulin secretion in the presence of a basal glucose concentration; rather, they only enhanced the secretion elicited by a stimulatory glucose concentration.

Recent study by Ghaly et al. (2014) explained why fluoroquinolones produce hypo- and hyperglycaemias, because fluoroquinolones affect the function of the mitochondria in pancreatic beta cells, which may diminish the insulinotropic effect of KATP channel closure and contribute to the hyperglycaemic episodes. In addition, ciprofloxacin and gatifloxacin cause oxidative stress and decrease the mitochondrial membrane potential (Lowes et al., 2009; Talla and Veerareddy, 2011; Rawi et al., 2011; Arafa et al., 2013). Gatifloxacin acutely diminish gluconeogenesis by inhibition of mitochondrial pyruvate transport (Drozak et al., 2008) since pancreatic beta cells have an exceedingly low antioxidant capacity (Lenzen et al., 1996) and inhibition of pyruvate transport may interfere with nutrient stimulation of insulin secretion. The study of Telfer (2014) extended to suggest a connection between the ingestion of fluoroquinolones antibiotics and the development of type 2 diabetes and advice that follow-up longitudinal studies to be undertaken to examine the history of individual diabetic patients for previous fluoroquinolone exposure. Glucose resuscitation resulting in hyperglycaemia activates the NADPH pathway in neurons, causing cytotoxic oxidative stress. The same phenomenon could also adversely affect oligodendrocytes (Suh et al., 2007). The study concluded from the recorded results that the excitatory potency of ciprofloxacin and gatifloxacin could be achieved from the first dose.

ACKNOWLEDGEMENT

The authors gratefully acknowledge the Department of physiology, NODCAR, Egypt.

Conflict of interests

The authors have declared that no competing interest exists.

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