National Journal of Physiology, Pharmacy and Pharmacology

RESEARCH ARTICLE

A comparative experimental study of proconvulsive potential of ciprofloxacin and ofloxacin and assessment of proconvulsive potentiating action of caffeine coadministration with fluoroquinolones in rats

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Received: September 14, 2017; **Accepted:** October 08, 2017

ABSTRACT

Background: Fluoroquinolones are one of the most common antimicrobials prescribed for a variety of infections. They have potential to lower seizure threshold. This can be harmful when prescribed to consumers of energy drinks as caffeine itself is a cortical stimulant. **Aims and Objectives:** The aim of this study is to compare proconvulsive potential of ciprofloxacin and ofloxacin in rats using pentylenetetrazole (PTZ) and maximal electroshock (MES) and to study potentiating effect of caffeine with fluoroquinolones. **Materials and Methods:** This study was performed in rats; 66 for MES and 66 for PTZ. In each model, 11 groups were made - normal saline, caffeine (2.5 and 5 mg/kg), ciprofloxacin (12.5, 25 and 50 mg/kg), ofloxacin (12.5, 25 and 50 mg/kg), ciprofloxacin 12.5 mg/kg + caffeine 2.5 mg/kg, and ofloxacin 12.5 mg/kg + caffeine 2.5 mg/kg. Each group had 6 rats. Duration of tonic hind limb extension (THLE) and clonic convulsions was noted for MES. The incidence of seizures, grade of convulsions, and onset of Grade 3 convulsions were noted for PTZ. **Results:** MES - prolongation of the duration of THLE and clonic convulsions was seen in caffeine 5 mg/kg, ciprofloxacin 50 mg/kg, and ofloxacin 25 and 50 mg/kg. Ciprofloxacin 12.5 mg/kg + caffeine 2.5 mg/kg and ofloxacin 12.5 mg/kg + caffeine 2.5 mg/kg significantly prolonged the duration of THLE and clonic convulsions in contrast to their individual administration ($P < 0.05$). PTZ - clonic convulsions with more than Grade 3 were seen in caffeine 5 mg/kg, ciprofloxacin 50 mg/kg, and ofloxacin 25 and 50 mg/kg. Ciprofloxacin 12.5 mg/kg + caffeine 2.5 mg/kg and ofloxacin 12.5 mg/kg + caffeine 2.5 mg/kg caused clonic convulsions higher than Grade 3 which were not seen on their individual administration ($P < 0.05$). **Conclusion:** Ofloxacin is more proconvulsive than ciprofloxacin. Combinations of low doses of ciprofloxacin with caffeine and ofloxacin with caffeine yielded convulsions which were not seen with individual drugs.

KEY WORDS: Ciprofloxacin; Ofloxacin; Caffeine; Convulsions; Maximal Electro Shock; Pentylenetetrazole

INTRODUCTION

Fluoroquinolones are one of the most frequently prescribed antimicrobials by physicians for almost any sort of infection, be it urological, sexually transmitted, respiratory or soft tissue infection; fluoroquinolones are among the most commonly used antibiotics.[1] While most clinicians are aware of the established side effects of fluoroquinolones related to the gastrointestinal tract, cardiovascular system, and skin. Adverse effects on central nervous system (CNS) also need to be explored as some CNS effects have been observed in some animal and clinical studies.[2-5] A headache and dizziness are common symptoms in humans. Hallucinations, delirium, and seizures have been observed in 0.9–11% of patients.[6] Potency to cause seizures is one of the most adverse toxic effects of fluoroquinolones. Fluoroquinolones cause seizures by antagonizing GABA action.[2,4]

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Website: www.njppp.com

DOI: 10.5455/njppp.2018.8.0935708102017

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Caffeine is a CNS stimulant belonging to methylxanthine group. It causes cortical stimulation, increased alertness, and allaying of fatigue.[7] Caffeine causes seizures by antagonizing adenosine receptors.[22] It is commonly found in coffee, tea, and high energy drinks. High energy caffeine drinks are very popular among today's youth and are considered as a running trend. Coffee has also been a favorite daily beverage among the young and old alike.

Due caution must be exercised when prescribing fluoroquinolones to coffee drinkers, and especially to youth, who are habituated to high energy drinks as caffeine and fluoroquinolone together may have synergistic proconvulsant effect. Young patients suffering from respiratory, urogenital, or cutaneous infections may require ciprofloxacin or ofloxacin to treat their infection. If they consume energy drinks and fluoroquinolone together, they run the risk of lowering their seizure threshold. As both caffeine and fluoroquinolone cause seizures different mechanisms of action. This is of concern, especially if fluoroquinolones have to be prescribed for a longer duration.

The current literature has established the potential of fluoroquinolones to cause convulsions, but literature is lacking in the concurrent use of fluoroquinolones and caffeine as to whether they do have any potentiating action.

The present study was done with the objective of comparing the proconvulsant action of two commonly prescribed fluoroquinolones - ciprofloxacin and ofloxacin and also to evaluate the proconvulsant potentiating effect of caffeine with ciprofloxacin and ofloxacin with the help of electroshock and chemoconvulsion models. Thus, a conclusion may be arrived as to which is safer among ciprofloxacin and ofloxacin and also whether it is safe to prescribe ciprofloxacin or ofloxacin to any individual who consumes coffee/caffeine in high quantity on a regular basis.

MATERIALS AND METHODS

The present study was done on 132 rats weighing between 100 and 200 g, procured from NIN, Hyderabad, and housed in animal house of Kamineni Institute of Medical Sciences, Narketpally, Nalgonda, Andhra Pradesh. The study was done during October 2011–September 2013. Prior approval was obtained from the Institutional Animal Ethics Committee of the same institute under the ICMR guidelines. Rats were kept in the animal house in polypropylene cages at a controlled temperature of 20–24°C and relative humidity of 50–60% with standard 12 h light-dark cycle beginning at 6.00 AM. They received standard pellet diet and water *ad libitum*.

Drugs - normal saline (Ranbaxy), caffeine (Loba chemie), ciprofloxacin (Ranbaxy), and ofloxacin (Ranbaxy) were used for the experiment. Caffeine solution of strength 2 mg/ml was prepared freshly on each day of experiment. Andrew and Laura have demonstrated that caffeine 5 mg/kg enhances electroshock convulsion.[8] Accordingly, we have given 5 mg/kg to one group and half dose (2.5 mg/kg) to another group for both models. Ciprofloxacin and ofloxacin were given in three graded doses of 12.5 mg/kg, 25 mg/kg, and 50 mg/kg.[2] Pentylenetetrazole (PTZ)(Hi-media)40 mg/kg was used for chemoconvulsion groups.[2] Fresh solution was prepared on each day of experiment by dissolving 50 mg of PTZ in 5 ml of distilled water. All drugs were given intraperitoneally.[2,9,10,12]

Rats were grouped in 22 groups having six rats in each group. Seizure induction was done using two models - electroshock and chemoconvuslion. Maximal electroshock (MES) by ear electrodes (techno) was used for the former, and PTZ was used for the latter.[11] 11 groups were allocated for electroshock and 11 for chemoconvulsion.

Group 1 was treated with normal saline and taken as control. Groups 2 and 3 were treated with caffeine 2.5 mg/kg and 5 mg/kg, respectively. Groups 4, 5, and 6 were treated with ciprofloxacin 12.5 mg/kg, 25 mg/kg, and 50 mg/kg, respectively. Groups 7, 8, and 9 were treated with ofloxacin 12.5 mg/kg, 25 mg/kg, and 50 mg/kg, respectively. Groups 10 and 11 were treated with combinations of caffeine 2.5 mg/kg with ciprofloxacin 12.5 mg/kg and ofloxacin 12.5 mg/kg, respectively. Groups 12–22 were grouped in the same manner for chemoconvulsion model but with different set of rats.

MES was given at 150 mA intensity for 0.2 s, 30 min after the intraperitoneal injection of test drug(s).[13] Duration of tonic hind limb extension (THLE) and duration of clonic convulsions were noted for the electroconvulsion groups. The dose of the drug(s) which increased the duration of THLE and duration of clonic convulsions was considered to have proconvulsant activity.[11] In the chemoconvulsion model, the incidence of seizures (1 = present, 0 = absent), Grade of convulsions (according to racene scale),[14] and the onset of Grade 3 convulsions (seconds) were noted.[14,15] Grading of convulsions according to Racene scale were as follows: 0 = no response, 1 = ear/mouth/facial twitchings, 2 = head nodding, 3 = forelimb clonus/body jerks, 4 = rearing, 5 = rearing, and falling down with/without generalized convulsions.[14,15] Higher incidence of seizures, higher grading of seizures, and reduction in onset of Grade 3 convulsions were considered as proconvulsant activity.[14,15]

Statistical analysis was done using one-way ANOVA, and *post hoc* test done by least significant difference method. SPSS v19 was employed for statistical analysis.

RESULTS

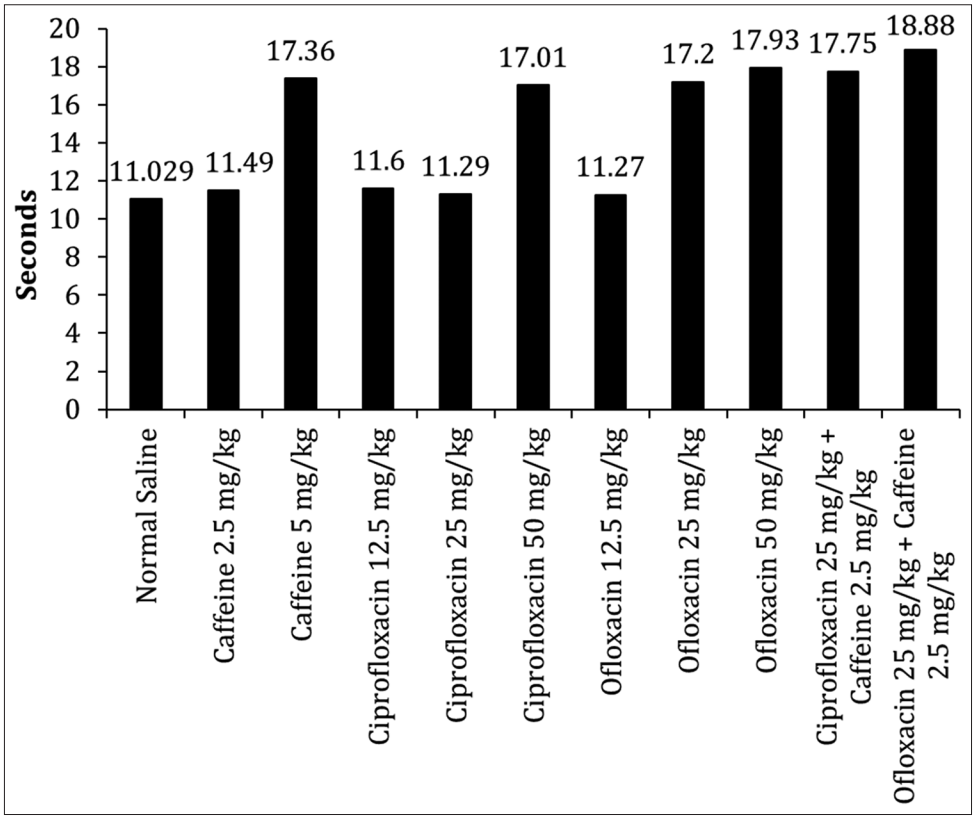
Electroshock Model

It was observed that caffeine 5 mg/kg significantly prolonged the duration of THLE (17.36 ± 0.87 s) and

duration of clonic phase (12.93 ± 0.42 s) in comparison to normal saline group, namely,. 11.02 ± 0.69 s and 5.01 ± 0.68 s, respectively ($P < 0.001$). While low dose of caffeine (2.5 mg/kg) did not prolong the duration of THLE (11.49 ± 0.44 s) or clonic convulsions (5.53 ± 0.40 s), and its effect was almost similar to that of normal saline ($P > 0.05$) [Table 1 and Graphs 1 and 2].

Among the fluoroquinolones, only ciprofloxacin 50 mg/kg significantly prolonged the duration of THLE (17.01 ± 0.58 s) and duration of clonic convulsions (13.01 ± 0.73 s) in comparison to normal saline group ($P < 0.001$). Effect of ciprofloxacin 50 mg/kg was similar to caffeine 5 mg/kg ($P > 0.05$) while lower doses of ciprofloxacin (12.5 mg/kg and 25 mg/kg) did not significantly alter the duration of THLE compared to normal saline group ($P > 0.05$) [Table 1 and Graphs 1 and 2].

Two doses of ofloxacin - 25 mg/kg and 50 mg/kg significantly prolonged the duration of THLE, i.e., 17.20 ± 0.61 s and 17.93 ± 0.80 s, respectively, in comparison to normal saline group ($P < 0.001$). Duration of clonic



Graph 1: Comparison of mean±standard deviation of the duration of tonic hind limb extension

Table 1: Comparison of mean±SD of the duration of THLE and clonic convulsions

Drug	Time (s)	
	Mean duration of THLE	**Mean duration of clonic convulsions**
Normal saline	11.02±0.69	5.01±0.68
Caffeine 2.5 mg/kg	11.49±0.44	5.53±0.40
Caffeine 5 mg/kg	17.36±0.87	12.93±0.42
Ciprofloxacin 12.5 mg/kg	11.60±0.68	5.24±0.64
Ciprofloxacin 25 mg/kg	11.29±0.51	5.25±0.40
Ciprofloxacin 50 mg/kg	17.01±0.58	13.01±0.73
Ofloxacin 12.5 mg/kg	11.27±0.46	5.41±0.44
Ofloxacin 25 mg/kg	17.20±0.61	12.86±0.60
Ofloxacin 50 mg/kg	17.93±0.80	13.66±0.50
Ciprofloxacin 25 mg/kg+caffeine 2.5 mg/kg	17.75±0.65	13.82±0.71
Ofloxacin 25 mg/kg+caffeine 2.5 mg/kg	18.88±0.44	14.64±0.67

THLE: Tonic hind limb extension, SD: Standard deviation

convulsions was also prolonged by these two doses, i.e., 12.86 ± 0.60 s and 13.66 ± 0.50 s for 25 mg/kg and 50 mg/kg, respectively, in comparison to normal saline group ($P < 0.001$). Effect of ofloxacin 25 mg/kg and 50 mg/kg was similar to caffeine 5 mg/kg ($P > 0.05$). Ofloxacin 12.5 mg/kg did not significantly alter the duration of THLE and clonic convulsions phase when compared to normal saline group ($P > 0.05$) [Table 1 and Graphs 1 and 2].

Among the combination groups, ciprofloxacin 12.5 mg/kg + caffeine 2.5 mg/kg significantly prolonged the duration of THLE (17.75 ± 0.65 s) and clonic phase (13.82 ± 0.71 s) in contrast to administration of only caffeine 2.5 mg/kg and only ciprofloxacin 12.5 mg/kg which did not yield any significant prolongation of THLE and clonic convulsion phase ($P < 0.001$). The potentiating effect of combination was significantly higher compared to normal saline and all doses of ciprofloxacin ($P < 0.001$) [Table 1 and Graphs 1 and 2].

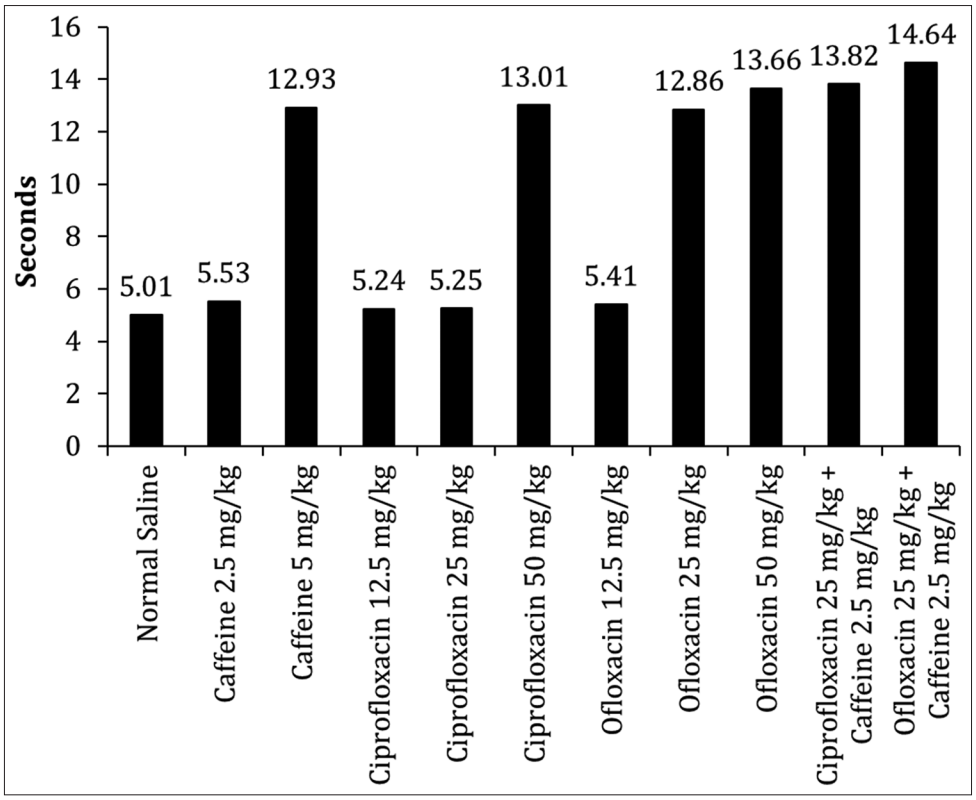
Ofloxacin 12.5 mg/kg + caffeine 2.5 mg/kg significantly prolonged the duration of THLE (18.88 ± 0.44 s) and clonic phase (14.64 ± 0.67 s) in contrast to administration of only caffeine 2.5 mg/kg and only ofloxacin 12.5 mg/kg which did not yield any significant prolongation of THLE and clonic convulsion phase ($P < 0.001$). The potentiating effect was significantly higher compared to normal saline, caffeine 5 mg/kg, all doses of Ofloxacin, and combination of ciprofloxacin 12.5 + caffeine 2.5 ($P < 0.05$) [Table 1 and Graphs 1 and 2].

Chemoconvulsion Model

It was observed that caffeine 5 mg/kg caused clonic convulsions in 6 of 6 rats (100%). Mean grade of convulsions was 4.67 ± 0.52 which was significantly higher in comparison to normal saline pretreatment which caused clonic convulsions in only 2 of 6 rats (33%) with a mean grade of 0.50 ± 0.84 ($P < 0.05$). Grade 3 convulsions in caffeine 5 mg/kg group started at 95.50 ± 3.94 s while Grade 3 convulsions were not attained in normal saline group. Low dose of caffeine (2.5 mg/kg) caused clonic convulsions in 2 of 6 rats (33%) with a mean grade of 0.55 ± 0.85, and its effect was almost similar to that of normal saline ($P > 0.05$) [Table 2 and Graph 3-5].

Among the fluoroquinolones, only ciprofloxacin 50 mg/kg caused clonic convulsions in 6 of 6 rats (100%). Mean grade of convulsions was 4.17 ± 0.75 which was significantly higher in comparison to normal saline pretreatment ($P < 0.05$). Grade 3 convulsions started at 96.50 ± 3.94 s. Effect of ciprofloxacin 50 mg/kg was similar to caffeine 5 mg/kg ($P > 0.05$) while lower doses of ciprofloxacin (12.5 mg/kg and 25 mg/kg) caused convulsions in 2 of 6 rats (33%). Mean grade of convulsions was 0.50 ± 0.52 and 0.57 ± 0.87, respectively, which were similar to that of normal saline ($P > 0.05$) [Table 2 and Graphs 3-5].

Ofloxacin 25 mg/kg and 50 mg/kg caused clonic convulsions in 6 of 6 rats (100%). Mean grade of convulsions were 3.67 ± 0.52 and 4.33 ± 0.82, respectively,



Graph 2: Comparison of mean±standard deviation of the duration of clonic convulsions

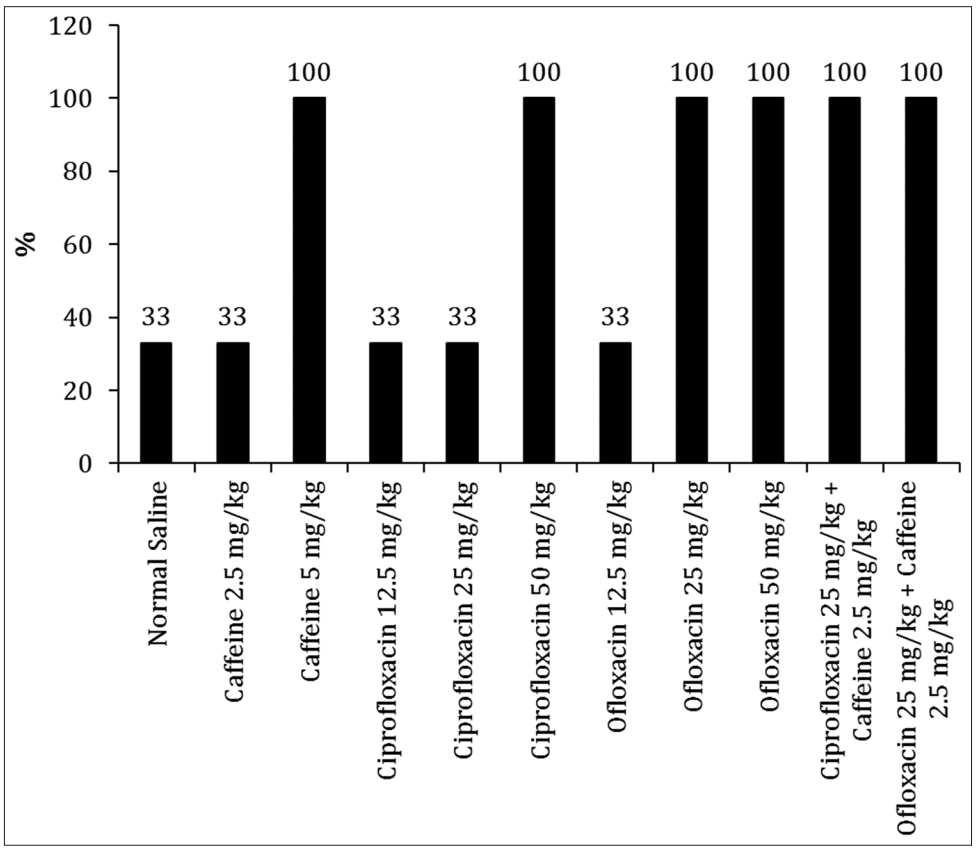
which were significantly higher in comparison to normal saline pretreatment ($P < 0.05$). Grade 3 convulsions started at 95.83 ± 3.06 s and 90.67 ± 3.33 s, respectively. Effect of these two doses of ofloxacin (25 mg/kg and 50 mg/kg) was similar to caffeine 5 mg/kg ($P > 0.05$). While lower dose of ofloxacin, i.e., 12.5 mg/kg, caused convulsions in 2 of 6 rats (33%). Mean grade of convulsions was 0.58 ± 0.77 which was similar to that of normal saline ($P > 0.05$) [Table 2 and Graphs 3-5].

Among the combination groups, ciprofloxacin 12.5 mg/kg + caffeine 2.5 mg/kg caused convulsions in 6 of 6 rats (100%) having a score of 4.67 ± 0.52 which is significantly higher in comparison to normal saline and also to their individual administrations ($P < 0.05$). Grade 3 convulsions started at 94.33 ± 3.93 s. Effect of this combination was similar to caffeine 5 mg/kg ($P > 0.05$). Combination of ofloxacin 12.5 mg/kg + caffeine 2.5 mg/kg caused convulsions in 6 of 6 rats (100%) having a score of 4.83 ± 0.41 which is significantly higher in comparison to normal saline and also to their individual administrations ($P < 0.05$). Grade 3 convulsions started at 90.00 ± 3.03 s. Effect of this combination was similar to caffeine 5 mg/kg ($P > 0.05$) [Table 2 and Graph 3-5].

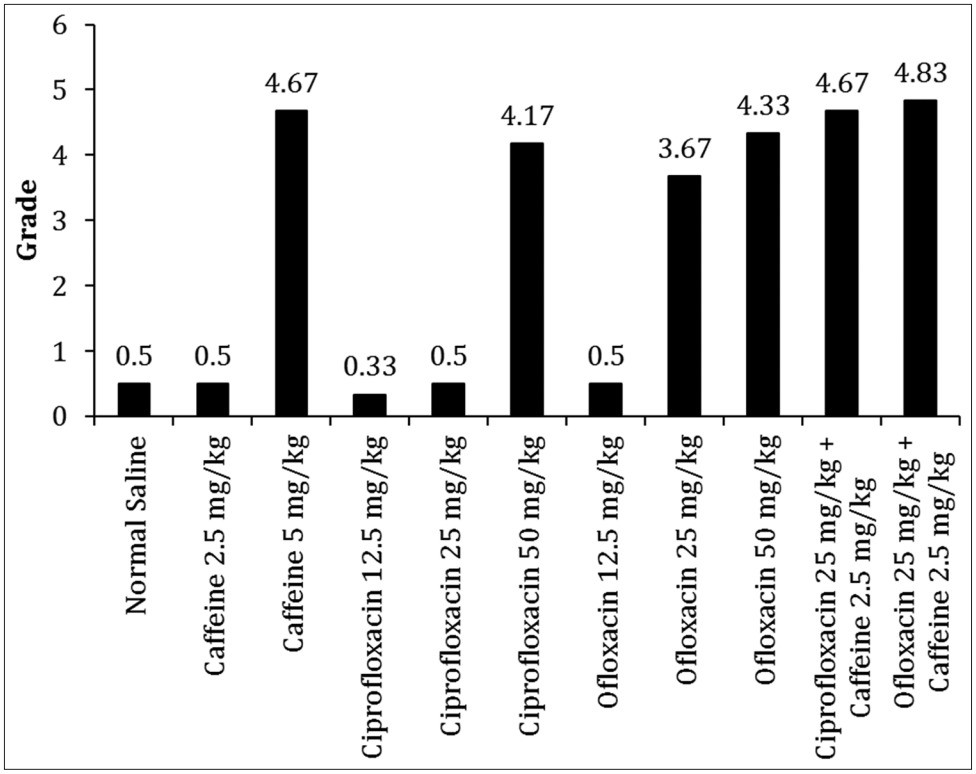
Table 2: Comparison of mean±SD of incidence of seizures, grade of convulsion, and onset of Grade 3 convulsions

Drug	Incidence (%)	Grade	Onset of Grade 3 convulsions (s)
Normal Saline	33	0.50±0.84	0
Caffeine 2.5 mg/kg	33	0.50±0.84	0
Caffeine 5 mg/kg	100	4.67±0.52	95.50±3.94
Ciprofloxacin 12.5 mg/kg	33	0.33±0.52	0
Ciprofloxacin 25 mg/kg	33	0.50±0.84	0
Ciprofloxacin 50 mg/kg	100	4.17±0.75	96.50±3.94
Ofloxacin 12.5 mg/kg	33	0.50±0.84	0
Ofloxacin 25 mg/kg	100	3.67±0.52	95.83±3.06
Ofloxacin 50 mg/kg	100	4.33±0.82	90.67±3.33
Ciprofloxacin 25 mg/kg+caffeine 2.5 mg/kg	100	4.67±0.52	94.33±3.93
Ofloxacin 25 mg/kg+caffeine 2.5 mg/kg	100	4.83±0.41	90.00±3.03

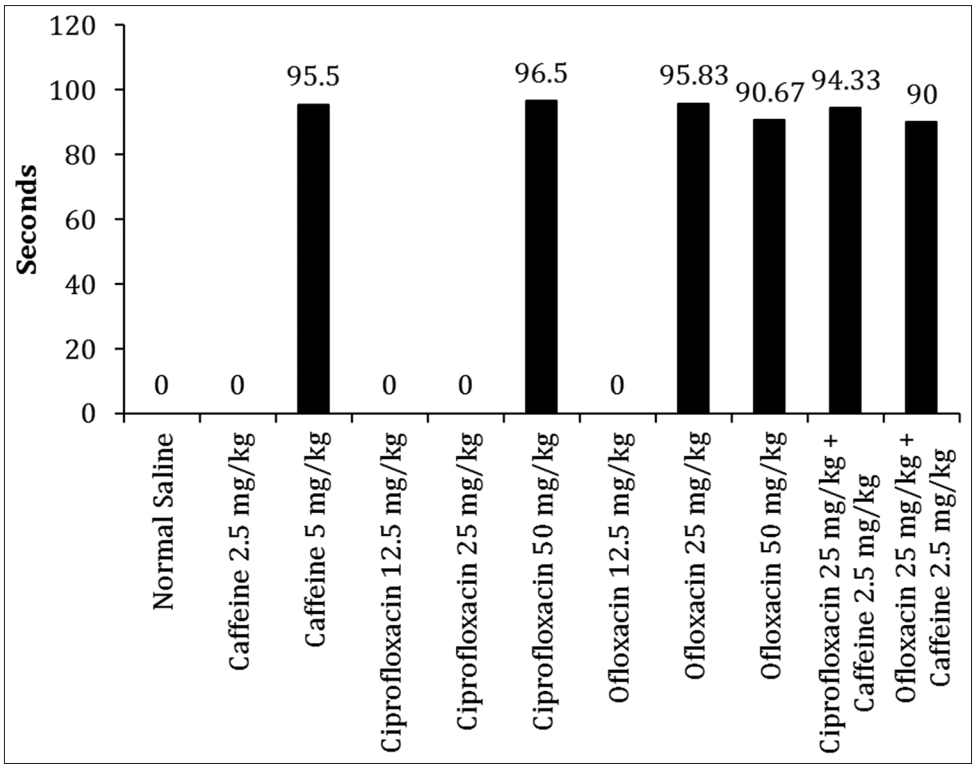
SD: Standard deviation



Graph 3: Comparison of incidence of seizures



Graph 4: Comparison of mean±standard deviation of grade of clonic convulsions



Graph 5: Comparison of mean±standard deviation of onset of Grade 3 convulsions

DISCUSSION

In this study, the effect of the ciprofloxacin and ofloxacin pretreatment on MES-induced seizures (150 mA for 0.2 s) and PTZ (40 mg/kg)-induced convulsions was observed. Both ciprofloxacin and ofloxacin pretreatment produced a significant increase in the duration of THLE and duration of clonic convulsions against MES-induced seizures in comparison to normal saline group, suggesting proconvulsant effect of ciprofloxacin and ofloxacin in MES model. Ofloxacin pretreatment in the dosage of 25 mg/kg i.p. produced a significant increase in duration of THLE and clonic convulsions

while ciprofloxacin pretreatment produced a significant increase in duration of THLE and clonic convulsions in the dosage of 50 mg/kg i.p. This suggests that ofloxacin is more potent proconvulsant than ciprofloxacin. In PTZ-induced clonic convulsions model, pretreatment with ciprofloxacin and ofloxacin produced a significant increase in the incidence and Grade 3 convulsions in comparison to normal saline pretreatment group. Further, the onset of clonic convulsions appeared significantly earlier with ciprofloxacin and ofloxacin pretreatment in the doses of 50 mg/kg and 25 mg/kg, respectively, suggesting proconvulsant activity of ciprofloxacin and ofloxacin in PTZ model in albino rats. In addition, ofloxacin appears more potent than ciprofloxacin as proconvulsant in PTZ model also like MES model, as a significant increase in incidence and Grade 3 clonic convulsions was observed with ofloxacin 25 mg/kg i.p., while dose required for ciprofloxacin was 50 mg/kg i.p., both the fluoroquinolones produced a dose-dependent proconvulsive effect, but ofloxacin had shown more proconvulsant potency than ciprofloxacin in MES and PTZ models. Lower doses of ciprofloxacin and ofloxacin in combination with subconvulsive dose of caffeine enhanced all parameters of MES and PTZ models, suggesting that ciprofloxacin and ofloxacin could potentiate the proconvulsant action of caffeine. The mechanism of CNS stimulant action of caffeine and fluoroquinolones are different. Proconvulsant activity of ciprofloxacin and ofloxacin is due to inhibition of GABA-A channels and lowering of seizure threshold as reported by De Sarro and De Sarro 2001.[4] Caffeine acts by blocking adenosine receptor in the brain.[22] Potentiation of proconvulsive action of fluoroquinolone is seen on addition of caffeine.

Our observations are supported by an earlier study done by Shalini and Prabhu 1999 who have also reported an increase in THLE in MES model with graded doses of ciprofloxacin and ofloxacin and also observed the increased occurrence of convulsions in PTZ model.[2] This similarity may be due to the usage of same species and same animal models, but they have not mentioned caffeine in their study.

From our study results, we would state that these antimicrobial agents should better be avoided for individuals habituated to energy drinks and also for patients predisposed to seizures such as those with history of convulsions, brain tumor, anoxia, metabolic imbalance, and psychotic episodes. Infections may be treated with alternative antimicrobial, or caffeine drink consumption should be avoided during treatment. However, our study is limited to animal models in single species. Results may vary from species to species and ultimately in humans.

Further studies are required in different species to establish potentiating the action of caffeine with fluoroquinolones. Long-term clinical studies are also needed to establish a safe dose range of fluoroquinolones for caffeine consumers and also for individuals predisposed to convulsions.

CONCLUSION

The present study suggests that ofloxacin has more proconvulsant potency than ciprofloxacin. in adition, a combination of low-dose ciprofloxacin with low-dose caffeine and combination of low-dose ofloxacin with low-dose caffeine has caused convulsions which were not seen when these were given individually. Further studies with different fluoroquinolones and different routes in different animal species are required to study this interaction of fluoroquinolones and caffeine. The findings thus obtained might need further support from clinical studies to study the effect of fluoroquinolones in patients suffering from convulsive disorders and usage of fluoroquinolones in persons consuming high quantities of caffeine-containing drinks to establish perfect safety and efficacy guidelines.

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How to cite this article: Ahmed FZ, Fazeelath G. A comparative experimental study of proconvulsive potential of ciprofloxacin and ofloxacin and assessment of proconvulsive potentiating action of caffeine coadministration with fluoroquinolones in rats. Natl J Physiol Pharm Pharmacol 2018;8(3):358-365.

Source of Support: Nil, **Conflict of Interest:** None declared.