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Effect of Ciprofloxacin and Sodium Valproate on Chemical Induced Seizures in Mice: An Acute Study

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ABSTRACT

To evaluate the effect of ciprofloxacin & ciprofloxacin with sodium valproate in PTZ induced seizures in mice. The animals were divided into 4 groups and each group consists of 6 animals. The first group received normal saline, the second received ciprofloxacin, the third received sodium valproate and the fourth group received ciprofloxacin 30minutes prior to sodium valproate. After 45 minutes, Pentylenetetrazole given to all the groups & animals were observed for next one hour for generalised tonic clonic seizures. The data was analysed using SPSS software & results were interpreted by comparing different groups using Students't' test. The P value of ≤0.05 considered to be statistically significant. Ciprofloxacin significantly decreased the onset & increased the duration of generalized tonic clonic seizures. When given in presence of sodium valproate, ciprofloxacin significantly decreased the onset of jerk, straub tail & generalized tonic clonic seizures while there was significant increase in the duration of generalized tonic clonic seizures. Ciprofloxacin decreases the threshold for seizures in predisposed mice, has proconvulsant effect & also diminishes the anti epileptic effect of sodium valproate.

Keywords: Pentylenetetrazole (PTZ), ciprofloxacin, seizures, epilepsy.

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INTRODUCTION

Epilepsy is a disorder of brain function characterized by the periodic and unpredictable occurrence of seizures. Seizures refer to a transient alteration of behaviour due to the disordered, synchronous, and rhythmic firing of populations of brain neurons. Epilepsy affects 0.8% of human population & is associated with enhanced excitatory and impaired inhibitory neurotransmission or abnormal electrical properties of the affected neurons. Gamma-Aminobutyric acid (GABA), the principal inhibitory neurotransmitter in the cerebral cortex, maintains the inhibitory tone that counterbalances neuronal excitation [1]. Many of patients (20%) are resistant to treatment with drugs [1,2] Most of antiepileptic drugs act by increasing GABAergic transmission & by prolonging sodium channel inactivation. Sodium valproate is a broad spectrum antiepileptic & one of the first-line drug in the treatment of primary generalized seizures and syndromes, but it is also effective in status epilepticus, other seizure, mania and bipolar disorder [1-3]. Though several mechanisms are involved in the antiepileptic activity of sodium valproate, but enhanced GABA-ergic activity plays a major role [3].

As the epileptic patients have to take antiepileptic drugs for a prolonged period so they may develop many other diseases like UTIs, upper respiratory tract infection, skin and soft tissue infection, dental pain and many other infectious diseases. To get rid of infectious diseases, fluoroquinolones are one of the widely used therapy. Among fluoroquinolones, Ciprofloxacin is mainly prescribed due to its wide spectrum of action & cost effectiveness. Among various adverse effects on the CNS, convulsions remain a serious problem. In fact, convulsions have been reported more frequently for individuals predisposed to epileptic seizures and for patients who have received both fluoroquinolones and either theophyline or certain nonsteroidal anti-inflammatory drugs [4]. It is demonstrated that quinolones potentiate the convulsants effects elicited by cefazolin or imipenem in mice [5]. It is well-known that quinolones competitively inhibit in vitro the binding of [^{3}H] γ-aminobutyric acid ([^{3}H] GABA), [^{3}H] muscimol, and [^{3}H] diazepam to benzodiazepine (BDZ)-GABA receptors in postsynaptic membranes in a concentration-dependent manner [6,7]. However, as GABA antagonists, quinolones could expect to be proconvulsant when given to animals in combination with an agent that blocks GABA-mediated inhibition, such as Pentylenetetrazole [8].

In the present study we intended to assess the precipitation of seizures in predispose subject due to ciprofloxacin & pre-treatment of ciprofloxacin on the protective effect of sodium valproate on chemical induced seizures in mice.

MATERIAL AND METHOD

Animals

Albino mice weighing about 25-35 gm bred in the central animal house were used for the study after having permission from institutional animal ethics committee. They are housed in clean, clear, polypropylene cages in groups of four and maintained at 24.0±2ºC with 12 hrs light and dark cycle and have free access to food and water ad libitum. The animals kept in

experimental lab, seven days prior to experiment to acclimatize laboratory conditions. Each mice used only once. Experiments conducted between 9:00 to14:00 hrs.
Procedures involving animals and their care were carried out in conformity with institutional guidelines and the policy and legal directives of the committee for purpose of Control and Supervision of Experiments on Animals (CPCSEA).

Drugs**:** Ciprofloxacin, Sodium valproate & Pentylenetetrazole

Pentylenetetrazole Induced Convulsions [14]

Animals were divided into 4 groups & each group consists of 6 animals. The first group received normal saline, the second group administered with ciprofloxacin, third group received sodium valproate and the fourth with ciprofloxacin and sodium valproate respectively. Thereafter, all groups were challenged with Pentylenetetrazole. All drugs are administered intraperitoneally. In acute study, vehicle/drugs were administered 30 minutes before the PTZ administration. Volume of saline kept same to volume of ciprofloxacin in all the groups. In fourth group, Ciprofloxacin administered 30minutes prior to sodium valproate which will be given 45 minutes before Pentylenetetrazole. All drug solutions were prepared immediately before injection. Animals were placed in Polypropylene cage and observed over the following 1 hr for the incidence and onset of generalized tonic clonic convulsions. Doses of vehicle, ciprofloxacin, sodium valproate and number of animals used in each group were mentioned below.

Groups (n = 6)	Treatment
I	Saline + PTZ (60mg/kg body wt)
II	Ciprofloxacin (50mg/kg body wt) + PTZ (60mg/kg body wt)
III	Sodium valproate (100mg/kg body wt) + PTZ (60mg/kg body wt) + Saline
IV	Ciprofloxacin (50mg/kg body wt) + Sodium valproate (100mg/kg body wt) + PTZ (60mg/kg body wt)

Behavioural Assessment

In PTZ induced convulsions, the end points include

1. The first generalised tonic-clonic seizure with loss of righting reflex
2. The first episode of continuous generalized tonic-clonic seizure with loss of righting reflex for at least 5 seconds
3. Onset of myoclonic jerks
4. Straub's tail.

Above mentioned parameters were observed for the next 1 hour. The data was analysed using SPSS software, groups were compared & results interpreted by unpaired students't' test. $P \leq 0.05$ considered to be statistically significant.

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RESULTS

Mean score for onset of myoclonic jerk, onset of straub tail, onset of generalized clonic seizures & duration of generalized clonic seizures (with loss of righting reflexes) among different groups were calculated [Table 1]. Group 1 & group 2 were compared to assess the effect of ciprofloxacin [Figure 1]. The means difference of time taken for the onset of jerk was 2.33(P≥0.05), for the onset of straub tail was 4.667 (P≥0.05), for the onset of generalised tonic clonic seizures was 18.33 (P≤ 0.05) & for duration of generalised tonic clonic seizures was –20.166 (P≤0.05) while comparing group 1 with group 2 [Table 2]. Group 3 & group 4 compared to assess how ciprofloxacin affect anti epileptic activity of sodium valproate [Figure 2]. The means difference of time taken for the onset of jerk was 49.33 (P≤ 0.05), for the onset of straub tail was 82.83 (P≤0.05), for the onset of generalised tonic clonic seizures was 76.16 (P≤0.05) & for duration of generalised tonic clonic seizures was -21.166 (P≤0.05) while comparing group 3 with group 4 [Table 2].

Table 1: Mean value of Effect of ciprofloxacin and sodium valproate on PTZ induced seizures in mice

Groups (n=6)	Onset of myoclonic jerks (Mean ± S.E.)	Onset of straub tail (Mean ± S.E.)	Onset of generalized tonic clonic seizure with loss of righting reflexes (Mean ± S.E.)	Duration of generalized tonic clonic seizure with loss of righting reflexes (Mean ± S.E.)
G1	79.66± 3.54	91.16 ± 2.37	113.66 ±6.37	60.83 ± 1.83
G2	77.33 ±3.86	86.50 ±3.73	95.33 ± 3.95	81.00 ± 5.03
G3	151.00 ± 14.63	221.66 ± 11.78	281.33 ± 21.22	18.66 ± 3.42
G4	101.66 ± 13.01	138.83 ± 12.28	205.16 ± 17.85	39.83 ± 6.98

Table 2: Comparison of mean difference of different groups

Parameter assessed	For **Group 1**(**PTZ**) v/s **Group 2**(**PTZ+ Ciprofloxacin**). Mean difference ±S.E. of mean difference	For **Group 3**(**PTZ+sodium valproate**) v/s **Group 4** (**PTZ+sodium valproate+ Ciprofloxacin**). Mean difference ±S.E. of mean difference
Onset of jerk	2.33±5.24 (P≥0.05)	49.33±19.58 (P<0.05)
Onset of straub tail	4.66±4.28 (P≥0.05)	82.83±17.02 (P≤0.001)
Onset of generalized tonic clonic seizures	18.33±7.50 (P<0.05)	76.16±27.73 (P<0.05)
Duration of generalized tonic clonic seizures	-20.16±5.35 (P<0.01)	-21.16±7.76 (P<0.05)

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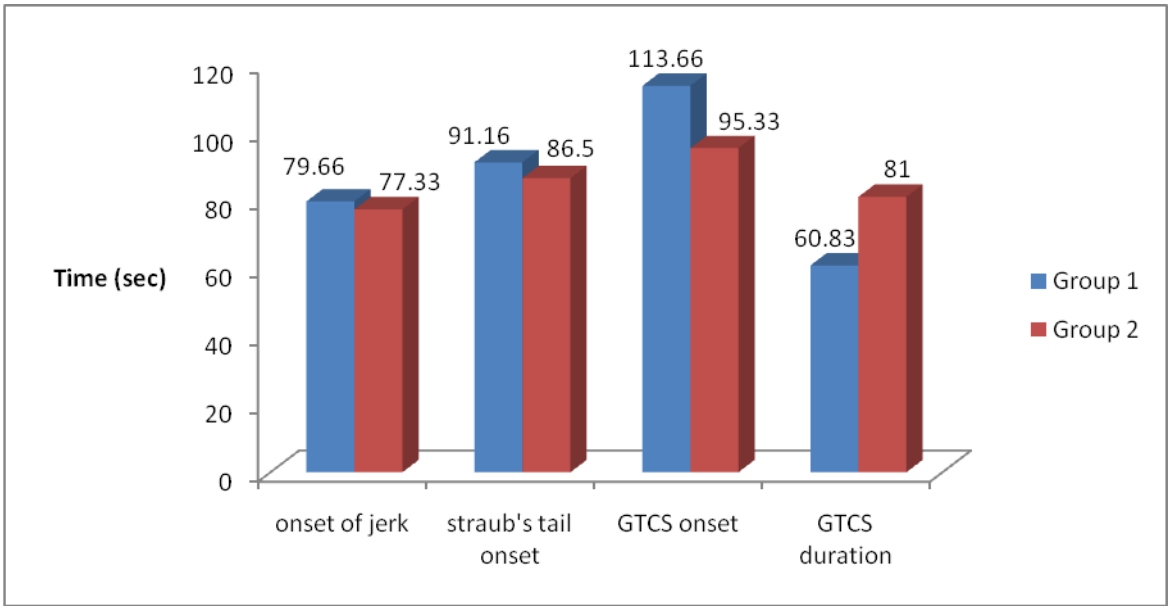

Figure 1: Comparison of Mean time taken in group 1 & group 2

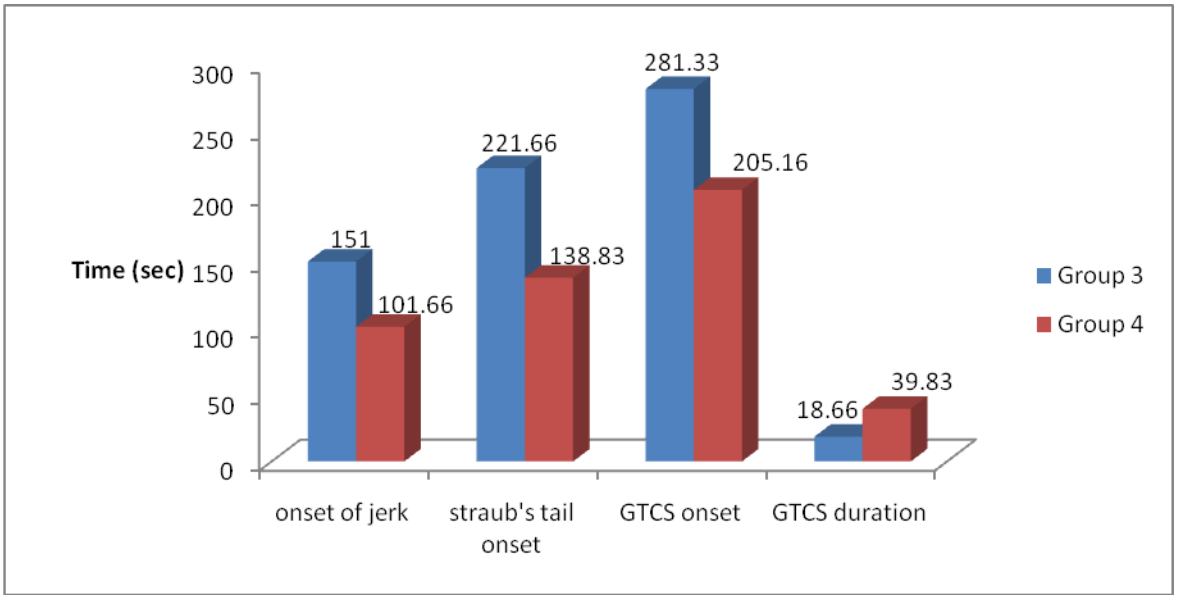

Figure 2: Comparison of Mean time taken in group 3 & group 4.

DISCUSSION

Ciprofloxacin significantly decreases the onset and increases the duration of generalized tonic clonic seizures (GTCS). In presence of proven antiepileptic sodium valproate, ciprofloxacin significantly decreases the onset of jerk, onset of straub's tail, onset of GTCS & increases the duration of GTCS. Our results demonstrated that ciprofloxacin has potential to increase the convulsant effects of PTZ & diminished the therapeutic effect of sodium valproate. These results are in agreement with those observed by Enginar and Eroglu [10], who demonstrated

that another fluoroquinolones (ofloxacin) reduced the threshold of convulsion induced by PTZ. Variety of studies regarding the CNS effects of quinolones have already been conducted, the mechanism of epileptogenic activity of quinolones is largely unresolved [6-9]. It was suggested by different authors that quinolones are able to increase the excitation of the CNS by inhibition of GABA binding to receptors resulting in enhanced convulsive activity [6-7]. Indeed, in contrast to the GABAergic mechanism, some authors suggested that other receptors, such as opioid and excitatory amino acid receptors, may also be involved in CNS effects of quinolones [7-12]. De Sarro G et al. demonstrated that drugs both enhancing GABAergic transmission and inhibiting excitatory amino acid transmission are able to antagonize seizures induced by pefloxacin in mice [12].

Therefore, a GABAergic mechanism is thought to be an essential part of but not the sole component of the mechanism by which quinolones induce seizures; glutamate is also suspected of being involved [11, 12].

In conclusion, Ciprofloxacin decreases the threshold for seizures in predispose mice, has proconvulsant effect & also diminishes the anti epileptic effect of sodium valproate. Ciprofloxacin must be used with caution in treating patients with predisposing epileptic factors or when the penetration of quinolones into the brain via a damaged blood-brain barrier is enhanced, due to its possible epileptogenic activity. The design and development of new quinolones derivatives with broader antibacterial activity, better pharmacokinetic properties and lesser or no CNS adverse effects should be developed to achieve therapeutic goals.

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