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INTERACTION OF CIPROFLOXACIN WITH DICLOFENAC AND PARACETAMOL IN RELATION TO IT's EPILEPTOGENIC EFFECT

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Abstract : A number of fluroquinolones have shown convulsive potential. The effect of Ciprofloxacin was studied in electroconvulsive seizures in mice using the tonic extensor phase as end point and seizure threshold as observational parameter. Its interaction with diclofenac and paracetamol was also studied. It was found that Ciprofloxacin produced a significant epileptogenic effect. This was potentiated by diclofenac but paracetamol had no such effect. Though the exact mechanisms involved in this effect are conjectural, role of GABA inhibitory mechanisms is a possibility.

Key words : fluoroquinolones ciprofloxacin mice seizure diclofenac paracetamol

INTRODUCTION

The adverse reactions of fluroquinolones have recently attracted a lot of attention. The C.N.S. toxicity is to the extent of 0.9 to 2% (1). Headache, dizziness, agitation, insomnia, hallucinations and delerium have been reported. Seizures occur rarely and there is a predisposing factor usually in the form of brain tumor, anoxia and metabolic imbalance (2). Tonic clonic convulsions have been reported in mice with enoxacin, lomefloxacin, ciprofloxacin and norfloxacin in doses ranging from 100 mg/kg to 1200 mg/kg (1, 3). Fluroquinolones are reported to be inhibitory on muscimol binding to GABA receptor sites (4). *In vitro* studies indicate that fenbufen, indomethacin, flurbiprofen and aspirin enhanced the inhibitory response of enoxacin and norfloxacin on GABA receptor sites. However, clinically seizures are reported more frequently with ciprofloxacin, norfloxacin and pefloxacin (1, 3).

In the present study, we have studied the response of ciprofloxacin on seizure threshold and it's possible interaction with diclofenac and paracetamol.

METHODS

Healthy adult mice of either sex, weighing 10-20 gms were used. They were housed in a group of 4 animals per cage and had a free access to tap water and a standard laboratory diet. The seizure threshold was determined by electroconvulsiometer (Inco Model No. C) as described by Swinyard (6). Electrodes applied to ear lobes of the animals were used for delivery of 60 cycles alternate current independent of external resistance. The duration of the stimulus was 0.2 sec. The technique to study seizure threshold was as described by Swinyard (6). The tonic extensor phase is taken as the end-point and the effect is seen as an all or none responses. The electro seizure threshold (E.S.T.)

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measurements were done on alternate days until the threshold was stabilized in about 15 days.

At the end of two weeks, it was found that out of 50 animals screened, 23 (46%) tested positive for tonic extensor phase with 15 mA current.

The 23 animals which showed tonic extensor phase with the current of mA were given different drug treatments as shown below. The interval between two drug administrations was one week.

The animals received - (1) ciprofloxacin 50 mg/kg, (2) ciprofloxacin 50 mg/kg + diclofenac 5 mg/kg and (3) ciprofloxacin 50 mg/kg + paracetamol 50 mg/kg.

All drugs were given by I.P. route 30 min prior to testing of seizure threshold. The doses used for all drugs were twice the usual single clinical dose in maximum volume of 0.5 ml.

In another set of study, 8 animals which tested positive for tonic extensor phase with current of 15 mA with ciprofloxacin alone were separately studied for tonic extensor phase after application of current of 12 mA after ciprofloxacin alone and also a combination of ciprofloxacin and diclofenac.

TABLE I : Effect of 15 mA current on animals tested for tonic extensor phase after different drug treatments.

Gr	*Drug treatment*	*No. of animals tested*	*Positive for tonic extensor phase*
1	Control	23	0
2	Ciprofloxacin	23	8*
3	Ciprofloxacin + Diclofenac	23	19**
4	Ciprofloxacin + Paracetamol	23	9*

*P < 0.05; **P <0.01

Data-Analysis

The % of animals showing tonic extensor phase after different drug treatments were calculated. The significance between different drug treatments was calculated by chi square test.

RESULTS

Table shows the effects of different drug treatments in mice which were tested for tonic extensor phase after the application of 15 mA current.

Results indicate that ciprofloxacin produced a convulsant effect which was significant ($P < 0.05$) as compared with control. Ciprofloxacin and diclofenac combination produced a still greater convulsant effect which was significantly more than ciprofloxacin alone ($P < 0.01$). In contrast to this paracetamol failed to increase the convulsant effect of ciprofloxacin as the effect of combination of ciprofloxacin and paracetamol was almost similar to the effect of ciprofloxacin alone.

In a separate set of experiments, the animals which showed convulsant effect with 15 mA current with ciprofloxacin alone were tested, none was +ve for tonic extensor phase. But after ciprofloxacin and diclofenac combination in the same animals, 5 animals tested +ve for tonic extensor phase. The difference was statistically significant ($P < 0.01$). This indicated that the combination of ciprofloxacin with diclofenac reduced the seizure threshold.

DISCUSSION

Chemically fluoroquinolones have a flourine atom in their molecules and either a piperazine or an aminopyrolidine moiety at 7

position of quinolone or naphthalidine ring, where the compounds seem to share the common structure with GABA agonists (not seen with nalidixic Acid (4). Fluroquinolones cause a concentration dependent competitive inhibition of GABA binding at post synaptic receptor sites. They may also cause a decreased release of GABA from nerve terminals, which is increased with NSAID group of drugs like fenbufen through its active metabolite biphenylacetate (6). The epileptogenic effect of norfloxacin was found to be suppressed by muscimol and diazepam which are agonists at GABA-A receptor sites but not by baclofen which is GABA-B agonist (4).

There is one report (7) that diclofenac had no effect on GABA receptor when given alone and had no additive effect with ciprofloxacin. But our study clearly shows that diclofenac has a potentiating effect on ciprofloxacin induced convulsant effect. To best of our knowledge there is no report of interactions of any of fluroquinolones with paracetamol. We also did not observe any significant effect of paracetamol on convulsant effect of ciprofloxacin.

The convulsant effect of fluoroquinolones has been correlated with GABA inhibiting mechanisms, though other mechanisms have also been proposed e.g.. dopaminergic, opiold and glutaminergic (8). Few pharmacokinetic studies have been done in rats. One of these (2) shows that when a combination of fenbufen and enoxacin was given in rats the enoxacin level ratio in plasma/brain as measured by H.P.L.C. was unaltered in presence of fenbufen. Another report (4) shows that plasma protein binding and plasma levels of lomefloxacin, ofloxacin and ciprofloxacin were not altered by fenbufen.

It therefore appears unlikely that in our study, the potentiating effect of diclofenac on ciprofloxacin induced convulsant effect and decrease in seizure threshold involves a pharmacokinetic mechanism, though we have not measured the plasma levels of ciprofloxacin. Whenever a combination of fluoroquinolones and NSAID group of drugs is given a close monitoring of patients is necessary. The present study, suggest that the combination of ciprofloxacin with paracetamol could be safer than that with diclofenac.

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