



PROCONVULSIVE POTENTIAL OF SOME FLUOROQUINOLONES ALONE AND WITH PARACETAMOL OR NIMESULIDE IN MICE

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ABSTRACT

The incidence of CNS adverse reaction with fluoroquinolones was 0.4 -4.4%. However, reports of neurological disturbances such as convulsion are rare. It is reported that some Prostaglandins synthesis inhibitors have lowered the threshold for convulsion. Nimesulide alone induce convulsion in high doses. Paracetamol is used generally in infections associated with fever and pain. Objectives of the present study i. to compare the epileptogenic potential of fluoroquinolones, ii. To compare that Nimesulide and paracetamol have any effect on epileptogenic potential of fluoroquinolones. Maximal electroshock seizures method and Pentylene tetrazole (PTZ) induced seizures method are used. Proconvulsive activity is increased with fluoroquinolone alone and in combination with paracetamol or nimesulide as compared to vehicle. Results of this study it has been seen that norfloxacin have more epileptogenic potential than sparfloxacin & sparfloxacin norfloxacin have more epileptogenic potential than ciprofloxacin. (i.e.N>S>C). When these quinolones were combined with paracetamol or nimesulide the potentiation of proconvulsive activity was observed but was not statically in significant. Hence fluoroquinolones should be prescribed cautiously in patients with history of convulsions. Patients who are also receiving NSAIDs should be carefully documented and administered fluoroquinolone carefully.

Keywords: Fluoroquinolones, Epileptogenic potential, Proconvulsive potential, Nimesulide.

INTRODUCTION

Since introduction in 1960s with nalidixic acid, quinolone antimicrobials have undergone extensive synthetic and clinical development resulting in improved antimicrobial activity, improved pharmacokinetic and toxic profile [1, 2]. Early quinolones had limited spectrum of activity, high frequency of bacterial resistance, frequently caused adverse event which virtually restricted their use to urinary tract infection [1, 3].

However, the most important breakthrough was development of fluoroquinolones in 2000 and 2010s. Recently new fluoroquinolone antimicrobials have been widely used in clinical field because of their high clinical safety. The adverse reactions to fluorinated quinolones mainly relate to gastrointestinal tract, central nervous system, skin, cardio toxicity, arthropathy and tendon toxicity [4, 5]. Clinical experience with fluoroquinolones have indicated that the incidence of CNS adverse reaction was 0.4 -4.4% [6]. The most frequently observed CNS symptoms are dizziness, headache, insomnia, restlessness

and more severe effects comprising hallucinations, confusion. However, reports of neurological disturbances such as convulsion are rare. They are almost associated with a predisposing factor such as brain tumor, anoxia or metabolic imbalance [7,8]. Tonic clonic convulsions have been reported in mice with lomefloxacin, ciprofloxacin and norfloxacin in the dose ranging from 100mg/kg to 1200mg/kg [8].

Prostaglandins have been reported to have anticonvulsive action and it is reported that some Prostaglandins synthesis inhibitors have lowered the threshold for convulsion [9]. The combination of fluoroquinolones and NSAIDs has additive effect in reducing the binding of GABA to its receptors [10]. Nimesulide is preferential cox-2 inhibitor, it is characterized by high anti-inflammatory, analgesic and antipyretic activity. Though it is said that it is banned, still available in the market and prescribed by the doctors. It is noted that nimesulide alone did not induce

convulsion at doses between 100-200mg/kg but induce clonic convulsions in dose dependent manner at doses ranging from 300-1600mg/kg [11].

Paracetamol is antipyretic analgesic and weak anti-inflammatory. Generally infections are associated with fever and pain .New fluoroquinolone have been used in clinical practice and are often used concomitantly with NSAIDs.

MATERIALS AND METHODS

The present study was undertaken in the Department of pharmacology, Government Medical College and hospital, Aurangabad after ethical approval from institutional animal ethics committee.

Source of animals

Mice bred in the central animal house Government Medical College and hospital, Aurangabad were used for the study. Animals were housed in colony cages with free access to food and water. The animals were acclimatized for 14 days before they were used for study.

Maximal electroshock seizures method

All animals were kept fasting overnight .Each mice received test drug orally 1 hr. before being subjected to electroshock of 48 mA for 0.2secs using ear clip electrodes. The duration in seconds of tonic hindlimb extension were noted. The increase in the duration of tonic hindlimb extension is considered as index of epileptic activity. Twenty four hour mortality if any is also recorded.

Pentylenetetrazole (PTZ) induced seizures method:

All animals were kept fasting overnight .Each mice received test drug orally 1 hr. before being subjected

to subconvulsive dose i.e. 40mg/kg of PTZ intraperitoneally. The animals were kept under observation for 30 min for latency of onset of seizures and development of colnic seizures. Rescue medicines given for uncontrolled tonic clonic convulsion was ether inhalation of ether and if not controlled with it then injection pentobabitone. Twenty four hour mortality if any was also recorded.

140 mice of either sex were used in the study (7 mice in each group).Total ten groups were made for Maximal electroshock seizures (MES) and ten groups for Pentylenetetrazole (PTZ) induced seizures were made. All drugs were suspended in the 2% gum acasia suspension.

Doses used for each drugs were Ciprofloxacin (130 mg/kg), Nimesulide (26 mg/kg), Paracetamol (130 mg/kg), Norfloxacin (104 mg/kg), Sparfloxacin (52mg/kg).

RESULTS

Table 1 shows the proconvulsive activity is increased with ciprofloxacin alone and in combination with paracetamol or nimesulide as compared to vehicle. Same results were seen for norfloxacin and sparfloxacin as compared to vehicle, but this increase in tonic hindlimb extension is not significant when compared ciprofloxacin alone with ciprofloxacin+Paracetamol or ciprofloxacin +Nimesulide. The same were for norfloxacin and sparfloxacin alone and its combination with paracetamol and nimesulide.

Table 2 shows significantly decreased latency (in seconds) for onset of convulsions (after PTZ 40mg/kg ip.inj.) when ciprofloxacin/norfloxacin /sparfloxacin alone were compared with vehicle. Latency for onset of seizures in norfloxacin gr. was lesser as compared to sparfloxacin and ciprofloxacin.

Groups made for MES seizures and PTZ induced seizures were as follows

Groups	
Control group (2% gum acasia as vehicle)	N+P: Norfloxacin+ Paracetamol
C: Ciprofloxacin	N+N: Norfloxacin+ Nimesulide
C+P: Ciprofloxacin+ Paracetamol	S: Sparfloxacin
C+N: Ciprofloxacin+ Nimesulide	S+P: Sparfloxacin+ Paracetamol
N:Norfloxacin	S+N: Sparfloxacin+ Nimesulide

Table 1. Tonic hindlimb extension in sec. after MES

	vehicle	C	C+P	C+N	N	N+P	N+N	S	S+P	S+N
Mean	9.671	11.583	11.597	11.768	20.579	21.009	22.001	17.260	17.281	16.580
STDEV	1.275	1.347*	2.343*	2.200*	3.236*#^	4.691*	4.134*	2.494*	2.860*	3.356*

^P<.05=Norfloxacin (N) compared with Sparfloxacin(S); #<0.01= Norfloxacin (N) compared with ciprofloxacin(C);

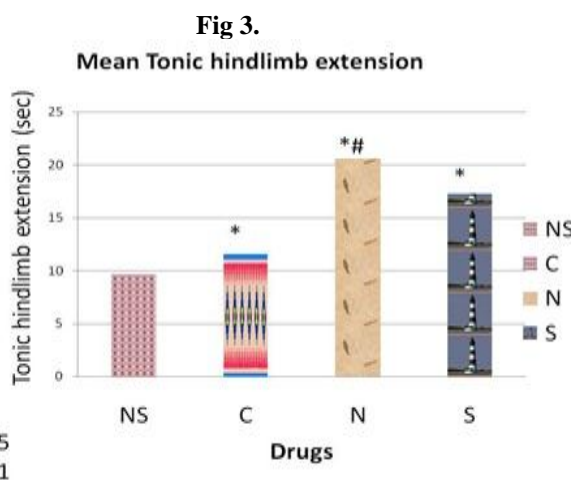
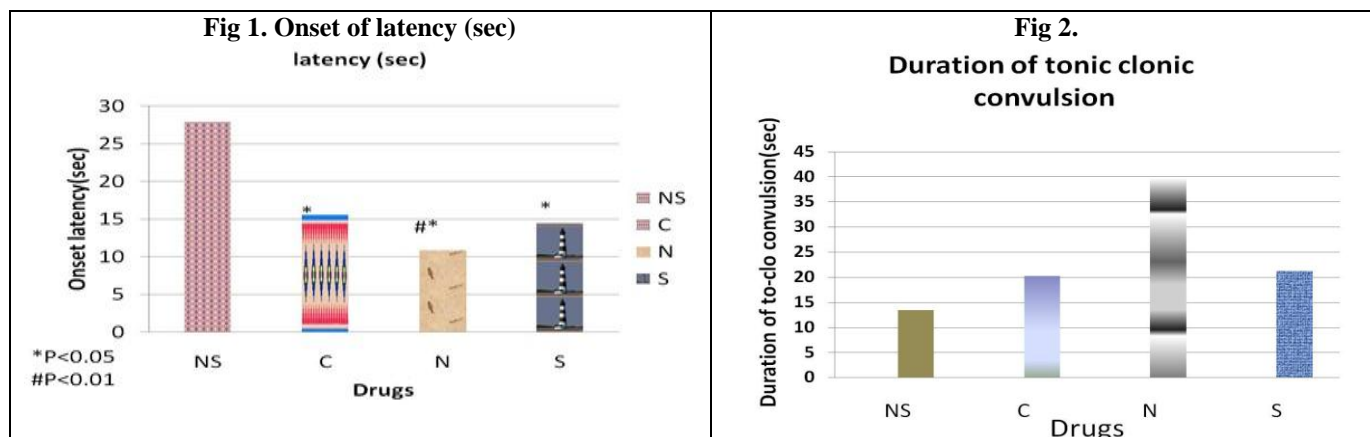
*<0.001=all groups compared with vehicle

Table 2. Latency of onset of seizure in sec after PTZ inj

	vehicle	C	C+P	C+N	N	N+P	N+N	S	S+P	S+N
Mean	27.857	15.571	15.143	14.124	10.857	11.429	10.571	14.429	13.571	12.429
STDEV	7.567	3.958*	3.642*	3.194*	2.231*^	3.155*	2.128*	4.065*	3.458*	3.200*

^P<.05=Norfloxacin (N) compared with Sparfloxacin(S); #<0.01= Norfloxacin (N) compared with ciprofloxacin(C);

*<0.001=all groups compared with vehicle



DISCUSSION AND CONCLUSION

Recent research in fluoroquinolone antibacterials has led to the discovery of number of compounds with greatly improved potency, spectrum, pharmacokinetic and clinical efficacy. But adverse effects these agents may cause gastrointestinal, central nervous system and cutaneous reaction, but these are usually mild and self limiting affecting 5-10% of patients only and rarely withdraw from therapy [12]. CNS disturbances are second most commonly reported adverse events with fluoroquinolone with an overall incidence of 1-2 %¹. Convulsion and seizures have occurred rarely and usually in setting of predisposing factors like epilepsy, cerebral trauma, anoxia, metabolic imbalance or concomitant therapy with interacting agents like theophylline and non steroidal anti-inflammatory agents.

Contradictory findings were observed in studies of S.Segev, M.Revehavi and E.Rubinstein [13] observed that diclofenac had no effect on GABA receptor when given alone and had no additive effect with ciprofloxacin. Whereas M.P.Shrivastva, S.D. Makde [14] observed that diclofenac has potentiating effects when combined with ciprofloxacin.

When these quinolones were combined with NSAID like paracetamol and preferential COX₂ selective agent like nimesulide, the potentiation of proconvulsive activity was observed but was not statically in significant. The exact mechanism of proconvulsive potential is not known, studies have shown that possible contributing mechanism for inducing convulsions is the strong binding of NSAIDs to protein which could influence the distribution of newer quinolones in the body and possibly enhance the transfer of newer quinolones in to the central nervous system.

In results of this study it has been seen that norfloxacin have more epileptogenic potential than sparfloxacin & sparfloxacin norfloxacin have more epileptogenic potential than ciprofloxacin. (i.e.N>S>C)

The exact mechanism by which quinolones induce seizures is controversial; however, there appears to be a strong association with similarities of structure of GABA. Some quinolones appear to displace or compete with GABA binding at receptor site within the CNS, resulting in CNS stimulation. Several researchers have demonstrated the associations between quinolones containing 7-piperazine (e.g., ciprofloxacin, enoxacin, and norfloxacin) and those containing 7-pyrrolidine (e.g., tosfloxacin and clinafloxacin) have increased epileptogenic potential. However, substituted methyl substituted 7-piperazinyl- or 7-pyrrolidinyl (e.g.,

levofloxacin, gatifloxacin, and sparfloxacin) are associated with reduced seizure-causing potential. There exists one exception—lomefloxacin—that contains a substituted piperazine group at position 7 and has been linked to seizures. This suggests a multifactorial contribution to this extreme form of toxicity. Quinolones with increased CNS penetration, coupled with unsubstituted piperazine or pyrrolidine groups at the 7 position, may be considered to be associated with a higher risk for seizures [15, 16].

Overall, quinolones with the potential for causing CNS-related adverse events may be listed, from greatest potential to least potential, as follows: fleroxacin, grepafloxacin, norfloxacin, sparfloxacin, ciprofloxacin, enoxacin, ofloxacin, pefloxacin, gatifloxacin, gemifloxacin, levofloxacin, and moxifloxacin. Spontaneous adverse event reports indicate that the incidence of CNS-related adverse events was higher in association with quinolone use (12.2%) than with the use of other systemic antimicrobials (3.6%; $P < .01$) [17].

Seizures are a rare occurrence but have been increasingly reported when used with theophylline or with NSAIDs. The occurrence frequency has been reported with trovafloxacin > norfloxacin > sparfloxacin > ciprofloxacin > ofloxacin > levofloxacin. Norfloxacin has

been associated with convulsions which may lead to an increase in intracranial pressure [18].

When it has been seen for CSF and brain tissue concentration of ciprofloxacin in human. For this 10 patients undergoing brain tumor excision were evaluated. The patients received a single intravenous dose of 400 mg ciprofloxacin. It has been seen that Ciprofloxacin concentrations 2 h after drug administration (analysed by HPLC method.) in plasma (0.87-2, 67 mcg/ml), in cerebrospinal fluid (0.7-0.37 mcg/ml) and brain tissue homogenate (0.65- 4, 02 mcg/g). This proves that ciprofloxacin achieves good concentration in brain tissue which may be one of the reason for increase in epileptic potential [19]. Thus to conclude, fluoroquinolones should be prescribed cautiously in patients with history of convulsions, brain tumour, anoxia, metabolic imbalance and psychotic episodes. Further more, such central nervous system effects in patients who are also receiving NSAIDs should be carefully documented and administration of either fluoroquinolone or Non Steroidal Antiinflammatory agent should probably be discontinued [20].

However, further long-term studies are needed with the use of these agents in clinical practice in diseased condition requiring long term therapy.

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