Pharmacology Biochemistry & Behavior, Vol. 39, pp. 587–589. © Pergamon Press plc, 1991. Printed in the U.S.A. 0091-3057/91 $3.00 + .00

The Effect of Ofloxacin and Ciprofloxacin on Pentylenetetrazol-Induced Convulsions in Mice

NURHAN ENGİNAR AND LÜTFIYE EROĞLU

Department of Pharmacology, Istanbul Faculty of Medicine, University of Istanbul, Çapa, Istanbul, Turkey

Received 23 January 1991

ENGİNAR, N. AND L. EROĞLU. *The effect of ofloxacin and ciprofloxacin on pentylenetetrazol-induced convulsions in mice.* PHARMACOL BIOCHEM BEHAV **39**(3) 587–589, 1991.—There have been several reports that convulsions, although rare, occur in patients who received fluoroquinolones. In this study, conducted for the evaluation of the convulsant action of fluoroquinolones, the effect of ofloxacin and ciprofloxacin on pentylenetetrazol-induced convulsions were investigated in mice. Mice were pretreated intraperitoneally (IP) with saline, ofloxacin (20 or 80 mg/kg) or ciprofloxacin (20 or 80 mg/kg) 30 minutes before subcutaneous (SC) administration of pentylenetetrazol (40 or 60 mg/kg). In another experiment, diazepam (5 mg/kg) was injected (IP) in mice alone or in combination with ofloxacin (80 mg/kg) 30 minutes before pentylenetetrazol (40 mg/kg) administration (SC). In each experiment mice were observed over the following hour for the incidence and onset of clonic convulsions. Results showed that both doses of ofloxacin increased the incidence of clonic convulsions induced by 40 mg/kg pentylenetetrazol. This effect, however was only significant in the higher dose and inhibited by diazepam. On the other hand, a similar proconvulsant effect by ciprofloxacin could not be demonstrated.

Fluoroquinolones Ofloxacin Ciprofloxacin Diazepam Pentylenetetrazol-induced convulsions

FLUOROQUINOLONES with a broad spectrum of antibacterial activity and excellent tissue penetrability have been used in the treatment of various infections. Although these drugs are presented with a low incidence of side effects (2,9), there have been several reports that even normal therapeutic doses can result in central nervous system (CNS) symptoms, primarily insomnia and convulsions, in some patients (6, 8, 10, 15, 19). Convulsions have been reported more frequently in individuals with underlying CNS predisposition and in patients who received both fluoroquinolones and either theophylline or certain nonsteroidal antiinflammatory drugs (11, 14, 18). Since it has been shown by different investigators (3, 7, 14) that fluoroquinolones caused concentration dependent inhibition of γ-aminobutyric acid (GABA) postsynaptic binding, fluoroquinolone-induced convulsions are suggested to be mediated at least in part through GABA receptors (3,17). Thus, as GABA antagonists, fluoroquinolones may potentiate the effect of convulsant drugs that appear to interact with GABA receptors. The aim of this study was therefore to investigate the effect of the fluoroquinolones, ofloxacin and ciprofloxacin, on pentylenetetrazol-induced convulsions in mice.

METHOD

Subjects

Inbred male albino mice weighing 20–25 g at the time of testing were used. The animals were housed under standard laboratory conditions for at least one week prior to experimentation and allowed free access to both water and food.

Drugs

Ofloxacin and ciprofloxacin were dissolved in distilled water and injected (IP). Pentylenetetrazol and diazepam were prepared in saline and given (SC) and (IP), respectively. All drug solutions, injected at a volume of 0.1 ml per 25 g body weight, were prepared immediately before injection.

Procedure

Experiment 1. On the day of testing, the animals were weighed and pretreated with 20 or 80 mg/kg ofloxacin, 20 or 80 mg/kg ciprofloxacin, or saline. Thirty minutes later the animals in the saline (control), ofloxacin and ciprofloxacin groups were injected with either 40 or 60 mg/kg pentylenetetrazol and then individually placed in wire-mesh cages. Mice were observed over the following hour for the incidence and onset of clonic convulsions. The animals were considered responsive to pentylenetetrazol when they displayed facial and forelimbs clonus with falling and straub tail phenomenon.

Experiment 2. Diazepam (5 mg/kg) was injected (IP) alone or concurrently with 80 mg/kg ofloxacin to another group of mice which were housed and maintained as described in Experiment 1. Thirty minutes later animals in each group received 40 mg/kg pentylenetetrazol (SC) and were observed over the following hour for the incidence and onset of clonic convulsions.

Statistical Analyses

A chi-square test was performed to determine if there were differences in the frequency of incidence of clonic convulsions due to pretreatment with different doses of ofloxacin or ciprofloxacin at the different dose levels of pentylenetetrazol. For the statistical evaluation of the onset of clonic convulsions, Student's *t*-test was used.

RESULTS

Table 1 shows that ofloxacin, not ciprofloxacin increased the incidence of clonic convulsions induced by 40 mg/kg pentylene-

TABLE 1

EFFECT OF OFLOXACIN AND CIPROFLOCAXIN ON PENTYLENETETRAZOL-INDUCED CLONIC CONVULSIONS IN MICE

Pretreatment	Dose	Pentylenetetrazol Dose	No. of Mice	Clonic Convulsion Incidence (%)	Clonic Convulsion Time of Onset (min) (Mean ± S.E.)
Saline	0.1 ml/25 g	40 mg/kg	20	15	8 ± 2.0
Ofloxacin	20 mg/kg	40 mg/kg	20	40	8 ± 1.8
Ofloxacin	80 mg/kg	40 mg/kg	20	45*	12 ± 1.8
Ciprofloxacin	20 mg/kg	40 mg/kg	20	20	13 ± 1.7
Ciprofloxacin	80 mg/kg	40 mg/kg	20	25	11 ± 1.8
Saline	0.1 ml/25 g	60 mg/kg	10	80	16 ± 2.6
Ofloxacin	20 mg/kg	60 mg/kg	10	80	10 ± 1.4
Ofloxacin	80 mg/kg	60 mg/kg	10	70	9 ± 1.4†
Ciprofloxacin	20 mg/kg	60 mg/kg	10	70	14 ± 2.8
Ciprofloxacin	80 mg/kg	60 mg/kg	10	80	9 ± 2.0

All mice were subcutaneously injected with pentylenetetrazol 30 minutes after an intraperitoneal drug injection.
*$p<0.05$, significantly different from saline group, Chi-square test.
†$p<0.05$, significantly different from saline group, Student's t-test.

tetrazol. This effect of ofloxacin however, was significant ($p<0.05$) only in the higher dose. On the other hand neither ofloxacin nor ciprofloxacin affected the incidence of clonic convulsions induced by 60 mg/kg pentylenetetrazol. Pretreatment with ofloxacin or ciprofloxacin had no apparent effect on the onset of clonic convulsions induced by 40 mg/kg pentylenetetrazol, while at the 60 mg/kg dose of pentylenetetrazol, the latency to onset of convulsions was significantly faster ($p<0.05$) in the 80 mg/kg ofloxacin-treated animals.

These fluoroquinolones did not exhibit any convulsant activity when administered alone in the same doses (data not shown).

Table 2 shows that diazepam inhibited both clonic convulsions induced by pentylenetetrazol alone and in combination with ofloxacin.

DISCUSSION

The results of the present study indicate that ciprofloxacin does not facilitate pentylenetetrazol-induced convulsions in mice. Failure to produce a proconvulsant effect was evident in each of the doses of ciprofloxacin tested. On the other hand ofloxacin reduced the threshold of pentylenetetrazol-induced convulsions. However, this effect of ofloxacin was only evident in the lower dose of pentylenetetrazol.

Agents that inhibit binding of GABA to its receptors have been associated with seizures in animal models (5). Inhibition of GABA mediated inhibitory transmission resulting in general excitation of the CNS may be the underlying mechanism of some proconvulsant drugs. It has been shown that ofloxacin and ciprofloxacin, as well as some other fluoroquinolones, caused concentration dependent inhibition of GABA postsynaptic binding (3, 7, 16). Thus these drugs could be expected to be proconvulsant when given to animals alone or in combination with an agent that blocks GABA mediated inhibition, such as pentylenetetrazol (12). However, neither ofloxacin nor ciprofloxacin exhibited any convulsant effects when given alone in the same doses (unpublished results). On the other hand, when given in combination with pentylenetetrazol, ofloxacin, but not ciprofloxacin, facilitated convulsions in mice in a dose dependent manner.

The present study was designed to demonstrate whether ofloxacin and ciprofloxacin act as proconvulsant agents. As ofloxacin potentiated pentylenetetrazol convulsions and this effect was reversed by diazepam, a GABA-mimetic drug (12), it seems that ofloxacin may possess a proconvulsant effect, presumably by inhibiting GABA. This suggestion is partly supported by our previous study that ofloxacin shortened sleeping time in pentobarbital-induced sleep in mice, presumably by interacting with GABA (4). In addition, in a clinical study suggesting that CNS adverse effects of ofloxacin could be mediated at least in part through interaction with GABA receptors, ofloxacin has been shown to have CNS-stimulating effects as revealed

TABLE 2

INHIBITORY EFFECT OF DIAZEPAM ON OFLOXACIN POTENTIATED CLONIC CONVULSIONS INDUCED BY PENTYLENETETRAZOL IN MICE

Pretreatment	Dose	Pentylenetetrazol Dose	No. of Mice	Incidence of Clonic Convulsion (%)
Diazepam	5 mg/kg	40 mg/kg	10	0
Diazepam + Ofloxacin	5 mg/kg + 80 mg/kg	40 mg/kg	10	0

All mice were intraperitoneally treated with diazepam alone or in combination with ofloxacin 30 minutes before a subcutaneous pentylenetetrazol injection.

by the electroencephalogram (EEG) which were reversed by coadministration of a benzodiazepine agonist (17).

On the other hand, a proconvulsant effect by ciprofloxacin could not be demonstrated in this study. As ciprofloxacin was found to provoke clonic convulsions in a previous study (1), before concluding the absence of a proconvulsant effect for ciprofloxacin in mice we may consider some reasons which would explain the present findings. First if there is an insufficient penetration into the mouse brain, then ciprofloxacin level in the CNS required to inhibit GABA binding to the receptor sites may not be achieved. Data from preclinical studies suggest that the fluoroquinolones cross the blood-brain barrier to a small extent (13). Second, the GABA antagonist potency of ciprofloxacin may be insufficient. Although in vitro binding studies show that the inhibitory potency of ciprofloxacin is greater than that of ofloxacin (1), the affinity of GABA receptors to ciprofloxacin in mouse brain may be less than those in the rat brain. Third, the underlying mechanism of convulsions induced by ciprofloxacin may involve systems in the CNS other than GABAergic system. However, lack of effect of ciprofloxacin on glutamate mediated neurotransmission (1) suggests that an involvement of excitatory amino acid mediated neurotransmission in the mediation of the proconvulsant effect is unlikely. And finally to vary the length of treatment and even the time of observation may be required for the appearance of ciprofloxacin's proconvulsant effect.

In conclusion, although additional studies are needed to determine the possibility of the proconvulsant effect of these fluoroquinolones, at least ofloxacin should be given cautiously to patients who may be sensitive to convulsant effects.

ACKNOWLEDGEMENTS

We thank Hoechst AG for the gift of ofloxacin and Bayer AG for the gift of ciprofloxacin.

REFERENCES

1. Akahane, K.; Sekiguchi, M.; Une, T.; Osada, Y. Structure-epileptogenicity relationship of quinolones with special reference to their interaction with α-aminobutyric acid receptor sites. Antimicrob. Agents Chemother. 33:1704–1708; 1989.
2. Blomer, R.; Bruch, K.; Kraues, H.; Wacheck, W. Safety of ofloxacin-adverse drug reactions reported during phase II studies in Europe and in Japan. Infection 14 (Suppl. 4):332–334; 1986.
3. Dodd, P. R.; Davies, L. P.; Watson, W. E. J.; Nielsen, B.; Dyer, J. A.; Wong, L. S.; Johnson, G. A. R. Neurochemical studies on quinolone antibiotics: Effects on glutamate, GABA and adenosine systems in mammalian CNS. Pharmacol. Toxicol. 64:404–411; 1989.
4. Enginar, N.; Eroğlu, L. Effect of ofloxacin on pentobarbital-induced sleep in mice. Eur. J. Pharmacol. 183:470–471; 1990.
5. Fisher, R. S. Animal models of the epilepsies. Brain Res. Rev. 14: 245–278; 1989.
6. Halkin, H. Adverse effects of the fluoroquinolones. Rev. Infect. Dis. 10 (Suppl. 1):S258–S261; 1988.
7. Hori, S.; Shimada, J.; Saito, A.; Miyahara, T.; Kurioka, S.; Matsuda, M. Effect of new quinolones on gamma-aminobutyric acid receptor binding. 25th Intersci. Conf. Antim. Agents Chemother. Minneapolis, abstract 396, 1985.
8. Janknegt, R. Fluorinated quinolones. A review of their mode of action, antimicrobial activity, pharmacokinetics and clinical efficacy. Pharm. Weekbl. Sci. Ed. 8:1–21; 1986.
9. Jüngst, G.; Rüdigar, M. Side effects of ofloxacin in clinical trials and in postmarketing surveillance. Drugs 34(Suppl. 1):144–149; 1987.
10. Monk, P. J.; Campoli-Richards, D. M. Ofloxacin: a review. Drugs 33:346–391; 1987.
11. Morita, H.; Maemura, K.; Sakai, Y.; Kaneda, Y. A case with convulsion, loss of consciousness and subsequent acute renal failure caused by enoxacin and fenbufen. Nippon Naika Gakkai Zasshi 74: 744–745; 1988.
12. Olsen, R. W. The GABA postsynaptic membrane receptor-ionophore complex. Site of action of convulsant and anticonvulsant drugs. Mol. Cell. Biochem. 39:261–279; 1981.
13. Sato, H.; Okezaki, E.; Yamamoto, S.; Nagata, O.; Kato, H.; Tsuji, A. Entry of the new quinolone antibacterial agents of ofloxacin and NY-198 into the central nervous system in rats. J. Pharmacobiodyn. 11:386–394; 1988.
14. Simpson, K. J.; Brodie, M. J. Convulsions related to enoxacin. Lancet ii:161; 1985.
15. Slavich, I. L.; Gleffe, R. F.; Haas, E. J. Grand epileptic seizures during ciprofloxacin therapy. JAMA 261:558–559; 1989.
16. Tsuji, A.; Sato, H.; Kume, Y.; Tamai, I.; Okezaki, E.; Nagata, O.; Kato, H. Inhibitory effects of quinolone antibacterial agents on γ-aminobutyric acid binding to receptor sites in rat brain membranes. Antimicrob. Agents Chemother. 32:190–194; 1988.
17. Unseld, E.; Ziegler, G.; Gemeinhardt, A.; Janssen, U.; Klotz, U. Possible interaction of fluoroquinolones with the benzodiazepine-$GABA_A$-receptor complex. Br. J. Clin. Pharmacol. 30:63–70; 1990.
18. Wang, C.; Sabbaj, J.; Corrado, M.; Hoagland, V. Worldwide clinical experience with norfloxacin: efficacy and safety. Scand. J. Infect. Dis. S48:81–82; 1986.
19. Wolfson, J. S. Quinolone antimicrobial agents: Adverse effects and bacterial resistance. Eur. J. Clin. Microbial. Infect. Dis. 8:1080–1092; 1989.