J. Pharm. Pharmacol. 1997, 49: 1025–1029
Received June 11, 1997
Accepted June 18, 1997

Interaction between Pefloxacin and Aminophylline in Genetically Epilepsy-prone Rats

C. IMPERATORE, G. R. TRIMARCHI AND A. DE SARRO

Institute of Pharmacology, School of Medicine, University of Messina, Italy

Abstract

The effects of a chronic treatment with pefloxacin on aminophylline-induced seizures in genetically epilepsy-prone rat have been investigated. Two series of experiments were performed. In the first, animals received pefloxacin orally twice a day for five days, then were administered aminophylline intraperitoneally and the occurrence of seizures was evaluated. In the second series of experiments, theophylline serum concentration was evaluated in rats subject to the same experimental protocol.

Pefloxacin significantly, and in a dose-dependent manner, increased the occurrence of seizure phases induced by aminophylline, but did not influence theophylline serum levels measured at different times after the injection of aminophylline.

We suggest that additive neurotoxic effects of both pefloxacin and aminophylline might contribute to the increased severity of seizure score. The possible role of GABA-benzodiazepine, excitatory amino acid and purinergic mechanism, and the role of pharmacokinetic factors are discussed.

Quinolones are a therapeutically important class of drugs with a broad spectrum of antibacterial activity. However, clinical evidence has indicated the possible incidence of undesirable adverse reactions and drug interactions after their use. In particular, the existence of significant drug interactions between fluoroquinolones and theophylline became evident shortly after the initiation of clinical investigations on these antibiotics (Maesen et al 1984; Wijnands et al 1986). Further studies documented a wide range of effects of different fluoroquinolones on the total clearance of theophylline, ranging from a 60% decrease with enoxacin to a non-significant effect with lomefloxacin (Ho et al 1988; Rogge et al 1988; Nix et al 1989), In-vitro studies indicated that these effects are a result of interaction of the fluoroquinolones with the cytochrome P-450-dependent microsomal metabolism of theophylline (Mulder et al 1988; Hasegawa et al 1990; Sarkar et al 1990).

Recently, we described the behavioural pattern of this interaction in the genetically epilepsy-prone (GEP) rat, a strain that represents a genetic model of epilepsy, developed by selectively inbreeding Sprague-Dawley rats, that elicited a particular susceptibility to audiogenic stimulation (Reigel et al 1986; Laird & Jobe 1987). This strain shows also enhanced susceptibility to convulsions induced by the administration of several convulsants (Faingold 1988; Frank et al 1989). Our studies also indicated the onset of a more severe convulsive symptomatology in GEP compared with Sprague-Dawley rats after the administration of aminophylline (De Sarro & De Sarro 1991). This different behaviour pattern might be related, at least in part, to the different pharmacokinetic profiles of aminophylline in Sprague-Dawley and GEP rats (Imperatore et al 1995).

To date, the mechanisms underlying the interaction between quinolones and theophylline are unclear. We postulated that fluoroquinolone–theophylline interaction is not only pharmacokinetic but also pharmacodynamic, thus the purpose of this study was to investigate further the mechanisms of such interaction in GEP rats. The study was designed to determine the effects of a multiple-dosing regimen of pefloxacin on the behaviour pattern induced by aminophylline and on the pharmacokinetics of theophylline.

Correspondence: C. Imperatore, Institute of Pharmacology, School of Medicine, University of Messina, Piazza Venti Settembre 4, 1-98122 Messina, Italy.

Materials and Methods

Animals

GEP rats (a strain derived from Sprague-Dawley rats) were inbred at the animal facilities of the Institute of Pharmacology at the University of Messina, from progenitors originally obtained from Dr B. S. Meldrum (University of London). All animals used in the study were male and 15–16 weeks old. Rats were housed under stable conditions of humidity (55 ± 5%), temperature (22 ± 1°C) and in a natural photo-period. The animals had unlimited access to standard laboratory rat chow (MIL, S. Morini, S. Polo D'Enza, RE, Italy) and tap water.

Drugs

Aminophylline was purchased from Sigma (Milan, Italy). Pefloxacin mesylate was obtained from Rhone-Poulenc Pharma (Milan, Italy). Aminophylline was dissolved in 0·15 M NaCl and administered intraperitoneally in a volume of 4 mL kg^{-1}; pefloxacin mesylate was administered orally in a volume of 4 mL kg^{-1}.

Testing of behavioural pattern

GEP rats were randomly assigned to either the pefloxacin-treatment groups (n = 24) or the vehicle-treatment groups (n = 24). The animals received 8 mg kg^{-1} pefloxacin or the corresponding volume of vehicle (0·15 M NaCl solution) twice a day, at 0800 h and 2000 h, by gastric intubation. This treatment was continued for 5 days. On day six both groups of rats received a last dose of pefloxacin or of vehicle 1 h before

intraperitoneal administration of aminophylline (90, 120 or 150 mg kg^{-1}). They were then placed in Plexiglas boxes (40 × 40 × 35 cm), and continuously observed for 6 h. The intensity of the seizure response was scored on the scale reported in the legend to Table 1.

Pharmacokinetic study

GEP rats were randomly assigned to either the pefloxacin-treatment group (n = 10) or the vehicle-treatment group (n = 10). The animals received 8 mg kg^{-1} pefloxacin or the corresponding volume of vehicle as describe above. On day six, after the last dose of pefloxacin or the same volume of vehicle, they were anaesthetized with diethyl ether and a catheter (PE50) filled with saline heparin (20 units mL) solution was inserted into the right jugular vein and exteriorized at the nape of the neck to enable drawing of blood. Animals were placed in single cages and were left for 120 min to recover from the anaesthesia. Subsequently, rats received 120 mg kg^{-1} aminophylline intraperitoneally. Blood samples (ca. 150 μL) were drawn from the venous catheter 0·25, 1, 1·25, 2, 3, 4 and 8 h after aminophylline administration. The blood was centrifuged at 1800 rev min^{-1} for 20 min and the serum was stored until theophylline assay. At the time of the assay the serum was diluted 10-fold with sterile 0·15 M NaCl solution. The assay was performed by use of an ACA Dupont model SX Automatic Analyser which uses a method based on a particle-enhanced turbidimetric inhibition immunoassay (Ryder et al 1983). The calibration curve was obtained by linear regression and was linear in the range 20–160 μg mL^{-1} (equation: $y = -7{\cdot}086426 + 1{\cdot}049405x$; correlation coefficient (r^2) 0·9999821). The precision expressed as relative standard deviation was 6·1% at 100 μg mL^{-1} and 5·7% at 120 μg mL^{-1}. The accuracy of the assay was between 5·4 and 14·48% within the calibration range, with a mean value of 8·5%. Changes in theophylline serum concentrations were studied according to a one-compartment model using SIPHAR/WIN software (Simed, Creteil Cedex, France). The parameters measured were the maximum theophylline concentration (C_{max}) and the time to reach this maximum (T_{max}). The half-life during the elimination phase ($t_{\frac{1}{2}}$) was determined from the terminal portion of the monoexponential concentration–time curve:

$$t_{\frac{1}{2}} = \ln(2)/K \quad (1)$$

Areas under plasma concentration–time curves (AUC) were computed from:

$$AUC = \{(K_a \times dose \times F)/V\}[\textstyle\sum_i (C_i/\{L_i - K_a\}[1/K_a]) + \sum_i (C_i/\{K_a - L_i\}[1/L_i])] \quad (2)$$

where L_i represents the exponents and C_i the coefficients, F is the bioavailability, K_a is the absorption rate constant and V is the volume of distribution. The mean residence time (MRT) was determined from:

$$MRT = MAUC/AUC \quad (3)$$

where:

$$MAUC = \{(K_a \times dose \times F)/V\}[\textstyle\sum_i (C_i/\{L_i - K_a\}[1/K_a^2]) + \sum_i (C_i/\{K_a - L_i\}[1/L_i^2])] \quad (4)$$

The clearance (Cl) was calculated from:

$$Cl = (dose/AUC) \times F \quad (5)$$

and the volume of distribution (β phase) was determined from:

$$Vd\beta/F = Cl/\beta \quad (6)$$

The parameters of the different phases of the curve were estimated by means of the peeling algorithm (Gomeni & Gomeni 1978).

The parameter estimates computed with the previously described method were used with a numerical algorithm based on the Powell (1964) method to minimize any objective function.

Statistics

Behavioural effects were analysed statistically by non-parametric methods. A Kruskall-Wallis analysis of variance was initially performed to test the behaviour pattern; if this was significant a Mann-Whitney *U*-test was used to compare behavioural effects in vehicle- and pefloxacin-treated rats. Each variable studied is presented as the median seizure score ± interquartile range.

The theophylline serum levels and the pharmacokinetic differences between the two groups of rats were assessed for significance by means of Student's *t*-test for unpaired data. Comparison between means of several populations was performed by analysis of variance.

Data are expressed as mean ± s.d.

A probability of less than 0·05 was considered as indicative of a significant difference.

Results

Behavioural differences between vehicle- and pefloxacin-treated rats in response to aminophylline

Repeated oral administration of pefloxacin (twice a day for five days and the last dose on day six), followed by a single intraperitoneal dose of aminophylline induced an increase in the severity of seizures in comparison with the group receiving vehicle plus aminophylline (Table 1). The median seizures score observed in rats treated with pefloxacin plus aminophylline was significantly higher ($P < 0{\cdot}01$) than that observed in rats treated with vehicle plus aminophylline.

Pharmacokinetics of theophylline

The concentrations of theophylline measured in the serum of vehicle- and pefloxacin-treated rats injected with 120 mg kg^{-1} aminophylline are presented in Table 2. No statistically significant difference between theophylline serum concentrations in vehicle- and pefloxacin-treated rats was observed at any of the time-points considered. Furthermore, none of the pharmacokinetic parameters calculated was significantly modified by administration of pefloxacin (Table 3). In fact, no significant changes in C_{max}, T_{max}, MRT, AUC_{exp}, $t_{\frac{1}{2}}$, clearance or volume of distribution were observed in the vehicle- and pefloxacin-treated groups.

Discussion

These results further support the reported interaction occurring between some quinolones and aminophylline. Several observations suggest inhibition of theophylline metabolism as the basis of this phenomenon. In fact, quinolones appear to be competitively inhibiting cytochrome P450 activity in the

Table 1. The effects of pefloxacin on seizures induced by aminophylline.

Treatment	Aminophylline dose (mg kg^{-1})	n	Median seizure score ± interquartile range			
			0–1 h	1–2 h	2–4 h	4–6 h
Vehicle	90	8	1·0 ± 1	1·0 ± 1	1·0 ± 1	1·0 ± 1
	120	8	2·0 ± 1	2·0 ± 1	2·0 ± 1	2·0 ± 1
	150	8	2·0 ± 1	3·0 ± 1	3·0 ± 1	4·0 ± 1
Pefloxacin	90	8	2·0 ± 1*	3·0 ± 1*	3·0 ± 1**	3·0 ± 1**
	120	8	3·0 ± 1*	4·0 ± 1*	5·0 ± 1**	5·0 ± 1**
	150	8	4·0 ± 1*	5·0 ± 1*	6·0 ± 1**	6·0 ± 1*

Rats were administered pefloxacin (8 mg kg^{-1}) or vehicle orally, twice daily for 5 days and again on the day of the test. One hour later they were injected intraperitoneally with the stated doses of aminophylline and observed for 6 h for occurrence of seizures. The incidence of each seizure phase was recorded; the median seizure score ± interquartile range for each dose studied is expressed. Seizure scoring scale: 0, no response; 1, wandering, twitching nose; 2, tremor, hind limb extension; 3, head nodding; 4, jumping, forelimb clonus; 5, forelimb clonus, rearing; 6, failing down; 7, tonic extension of all four limbs; 8, clonic-tonic seizures followed by post-ictal period or fatal outcome. *$P < 0.05$, **$P < 0.01$, significant differences between the incidence of seizure phases in pefloxacin-treated and vehicle-treated GEP rats (Mann-Whitney U-test).

Table 2. The effects of pefloxacin on theophylline serum levels (μg mL^{-1}).

	Time after injection of aminophylline (min)						
	15	60	75	120	180	240	480
Vehicle	96·32 ± 5·54	127·31 ± 10·38	146·12 ± 11·22	114·98 ± 9·87	104·64 ± 8·99	100·31 ± 9·12	46·88 ± 6·11
Pefloxacin	98·65 ± 5·99	123·82 ± 8·13	144·56 ± 8·10	119·40 ± 11·28	106·53 ± 8·95	98·46 ± 5·30	49·84 ± 6·45

Rats were administered pefloxacin (8 mg kg^{-1}) or vehicle orally, twice daily for 5 days and again on the day of the test. One hour later they were injected intraperitoneally with aminophylline (120 mg kg^{-1}). Theophylline serum levels (μg mL^{-1}) were measured at different times after the injection. Each value is the mean ± s.d. of results from 10 animals. Note that no differences were observed between serum theophylline levels of rats treated with pefloxacin or vehicle.

hepatic microsomes that also metabolize theophylline. Some quinolones, and in particular their metabolite 4-oxoquinolone, seem to be the main causes of the changes in theophylline metabolic clearance owing to competitive inhibition of the *N*-demethylation pathway of theophylline (Wijnands et al 1986; Hasegawa et al 1990).

On the other hand, elevated serum concentrations of theophylline have been reported when the compound was administered together with some quinolones (Maesen et al 1984; Wijnands et al 1986; Raoof et al 1987; Neu 1988) and seizures have also been observed in patients not showing elevated serum concentrations of theophylline (Ball 1986). Furthermore, our data clearly indicate that no significant changes occur in theophylline pharmacokinetics in GEP rats treated with aminophylline after repeated treatment with pefloxacin. These observations all suggest that pefloxacin causes an increase in the aminophylline-induced seizures without affecting the pharmacokinetics of theophylline. This enables us to theorize that additive neurotoxic effects of both compounds (theophylline and quinolones) might contribute to the increase of seizure score observed in our experimental model, especially taking into consideration the reported interaction between some quinolones and several neurotransmitter systems, i.e. GABA, dopamine, opioid and glutamate (Segev et al 1988; Dimpfel et al 1991). In fact, in-vitro studies indicated that quinolones might be acting by inhibiting the binding of GABA to its receptor sites (Segev et al 1988; Tsuji et al 1988; Akahane et al 1989). In particular, because the epileptogenic activity of some quinolones was suppressed by compounds enhancing GABAergic neurotransmission, for example muscimol and diazepam, which are agonists for the $GABA_A$-benzodiazepine receptor complex, whereas it was influenced only by neurotoxic doses of baclofen, a $GABA_B$ receptor agonist, the epileptogenic activity of quinolones might involve the $GABA_A$-benzodiazepine receptor complex (Tsuji et al 1988; Akahane et al 1989; Unseld et al 1990). In addition, in-vivo studies indicated that dopamine, opioid and glutamergic receptors might also be involved in the effects of quinolones on the CNS (Dimpfel et al 1991; William & Helton 1991). Because quinolones are chemically similar to kynurenic acids which might be endogenous ligands for excitatory amino acid receptors (Stone 1982), we might postulate possible interaction of quinolones with glutamate receptor binding sites. It is likely that excessive activation of excitatory amino acid receptors occurs secondary to or concomitantly with the impairment of the inhibitory GABAergic neurotransmission by pefloxacin and is essential for the propagation of seizures. This observation is in accord with a previous study showing that the proconvulsive activity of some quinolones might be antagonized by excitatory amino acid antagonists (William & Helton 1991). The possibility that pefloxacin possesses agonist or modulatory properties at receptors activated by excitatory amino acids might be an alternative explanation to the GABAergic one; this requires experimental confirmation.

Another point that should be taken in consideration is the possible connection between the lipophilic character of qui-

Table 3. The pharmacokinetics of theophylline.

Variable	Vehicle-treatment group	Pefloxacin-treatment group
Body weight (g)	287·9 ± 40·8	290·8 ± 39·7
Half-life during the elimination phase (h)	4·82 ± 0·70	5·03 ± 0·47
Area under the plasma concentration-time curve (h μg mL^{-1})	1078·6 ± 104·3	1105·3 ± 91·7
Maximum theophylline concentration (μg mL^{-1})	149·67 ± 8·79	144·56 ± 8·10
Time to reach maximum theophylline concentration (h)	1·20 ± 0·10	1·25 ± 0·00
Mean residence time (h)	6·75 ± 0·87	7·27 ± 0·76
Total clearance (mg (h μg mL^{-1})$^{-1}$)	0·112 ± 0·010	0·109 ± 0·009
Volume of distribution (mg (μg mL^{-1})$^{-1}$)	0·772 ± 0·056	0·789 ± 0·041

Rats were administered pefloxacin (8 mg kg^{-1}) or vehicle orally, twice daily for 5 days and again on the day of the test. One hour later they were injected intraperitoneally with aminophylline (120 mg kg^{-1}). Each value is the mean ± s.d. of results from 10 experiments.

nolones and the occurrence of central nervous system reactions. Pefloxacin is, in fact, the most lipophilic of the newer quinolones and effectively penetrates brain tissue and cerebrospinal fluid (Dalhoff 1989; Gonzales & Henwood 1989). Therefore, we suggest the possibility that the seizure-like activity induced by high doses of pefloxacin might be related to slow clearance of the drug from the cerebral area. With regard to the possible pharmacokinetic interaction between pefloxacin and aminophylline, studies performed in different animal species showed that the major metabolites of pefloxacin in rat plasma, urine and bile are pefloxacin glucuronide, pefloxacin *N*-oxide and norfloxacin (Montay et al 1984). Thus we suggest that because the extent of inhibition of theophylline metabolism was correlated mainly with the amount of 4-oxo-metabolite produced from the various quinolones, pefloxacin, with a low level of 4-oxo-metabolite had no apparent effect. This conclusion is in agreement with previous studies on the interaction of quinolones with aminophylline (Wijnands et al 1986; Hasegawa et al 1990) and corroborates the suggestion of an additive neurotoxic effect of both theophylline and pefloxacin.

With regard to aminophylline, a pivotal role in aminophylline-induced seizures might be played by GABA and glutamate, as reported in a number of experimental models of seizure (Corradetti et al 1984; Segev et al 1988), but the findings that methylxanthines are antagonists of adenosine action have led to the general conclusion that the seizure-like activity of aminophylline might be linked to its ability to antagonize the actions of endogenous adenosine. Furthermore, adenosine also inhibits the release of different types of transmitter, including glutamate and aspartate (Fredholm & Hedqvist 1980; Daly et al 1981; Dunwiddie et al 1981).

In conclusion, several factors, such as pefloxacin diffusion through the blood-brain barrier and the pharmacodynamic mechanisms of both pefloxacin and aminophylline need to be considered in attempts to explain the dangerous adverse effects that might arise from this interaction. In addition, the animal model used in this study enables us to suggest that physicians should consider the possible epileptogenic activity of the concomitant administration of aminophylline and pefloxacin when treating patients with predisposing epileptic factors.

References

Akahane, K., Sekiguchi, M., Une, T., Osada, Y. (1989) Structure–epileptogenicity relationship of quinolones with special reference to their interaction with gamma-aminobutyric acid receptor sites. Antimicrob. Agents Chemother. 33: 1704–1707

Ball, P. (1986) Ciprofloxacin: an overview of adverse experiences. J. Antimicrob. Chemother. 18: 187–193

Corradetti, R., Lo Conte, R., Moroni, F., Passani, M. B., Pepeu, G. (1984) Adenosine decreases aspartate and glutamate release from rat hippocampal slices. Eur. J. Pharmacol. 104: 19–26

Dalhoff, A. (1989) A review of quinolone tissue pharmacokinetics. In: Fernandes P. B. (ed.) Quinolones. J. R. Prous Science Publishers S. A., Barcelona, pp 277–312

Daly, J. M., Bruns, R. F., Snyder, S. H. (1981) Adenosine receptors in the central nervous system: relationship to the central actions of methylxanthines. Life Sci. 28: 2083–2097

De Sarro, A., De Sarro, G. B. (1991) Responsiveness of genetically epilepsy-prone rats to aminophylline-induced seizures and interactions with quinolones. Neuropharmacology 30: 169–176

Dimpfel, W., Spuler, M., Dalhoff, A., Hoffman, W., Schluter, G. (1991) Hippocampal activity in the presence of quinolones and fenbufen in vitro. Antimicrob. Agents Chemother. 35: 1142–1146

Dunwiddie, T. V., Hoffer, B. J., Fredholm, B. B. (1981) Alkylxanthines elevate hippocampal excitability. Naunyn-Schmiedebergs Arch. Pharmacol. 316: 326–330

Faingold, C. L. (1988) The genetically epilepsy-prone rat. Gen. Pharmacol. 19: 331–338

Frank, J. E., Ginter, K. L., Schwartzkroin, P. A. (1989) Developing genetically epilepsy-prone rats have an abnormal seizure response. Epilepsia 30: 1–6

Fredholm, B. B., Hedqvist, P. (1980) Modulation of neurotransmission by purine nucleotides and nucleosides. Biochem. Pharmacol. 29: 1635–1645

Gomeni, C., Gomeni, R. (1978) IGPHARM: interactive graphic package for pharmacokinetic analysis. Comp. Biomed Res. 11: 345–361

Gonzalez, I. P., Henwood, I. M., (1989) Pefloxacin. A review of its antibacterial activity, pharmacokinetic properties and therapeutic use. Drugs 37: 717–721

Hasegawa, T., Nadai, M., Kuzuya, T., Muraoka, I., Apichartpichean, R., Takagi, K., Miyamoto, K. (1990) The possible mechanism of interaction between xanthines and quinolones. J. Pharm. Pharmacol. 42: 767–772

Ho, G., Tierney, M. G., Dales, R. E. (1988) Evaluation of the effect of norfloxacin on the pharmacokinetics of theophylline. Clin. Pharmacol. Ther. 44: 35–38

Imperatore, C., De Sarro, G. B., De Luca, R., Trimarchi, G. R., De Sarro, A., Costa, G. (1995) Differences in the pharmacokinetics of aminophylline between genetically epilepsy-prone and normal Sprague-Dawley rats. Pharm. Sci. 1: 145–149

Laird, H., Jobe, P. C. (1987) The genetically epilepsy-prone rat. In: Jobe, P. C., Laird, H. (eds) Neurotransmitters and Epilepsy. Humana Press, Clifton, NJ, pp 57–89

Maesen, F. P. V., Teengs, J. P., Baur, C., Davies, B. I. (1984) Quinolones and raised plasma concentrations of theophylline. Lancet 2: 530

Montay, G., Goueffon, Y., Roquet, F. (1984) Absorption, distribution, metabolic fate, and elimination of pefloxacin mesylate in mice, rats, dogs, monkeys, and humans. Antimicrob. Agents Chemother. 25: 463–472

Mulder, G. J., Nagelkerke, J. F., Tijdens, R. B., Wijands, W. J. A., Van Der Mark, E. J. (1988) Inhibition of the oxidative meta-

bolism of theophylline in isolated rat hepatocytes by the quino-lone antibiotic enoxacin and its metabolite oxo-enoxacin, butnot by ofloxacin. Biochem Pharmacol. 37: 2565–2568

Neu, H. C. (1987) Clinical use of the quinolones. Lancet 82: 1319–1322

Nix, D. E., Norman, A., Schentag, J. J. (1989) Effect of lomefloxacin on theophylline pharmacokinetics. Antimicrob. Agents Chemother. 33: 1006–1008

Raoof, S., Wollschlager, C., Faroque, A. K. (1987) Ciprofloxacin increases serum levels of theophylline. Am. J. Med. 82: 115–118

Reigel, C. E., Dailey, J. W., Jobe, P. C. (1986) Neurobiology of seizure predisposition—the genetically epilepsy-prone rat. 1. The genetically epilepsy-prone rat: an overview of seizure-prone characteristics and responsiveness to anticonvulsant drugs. Life Sci. 39: 763–774

Rogge, M. C., Solomon, W. R., Sedman, A. J., Welling, P. G., Toothaker, R. D., Wagner, J. G. (1988) The theophylline-enoxacin interaction: 1. effect of enoxacin dose size on theophylline disposition. Clin. Pharmacol. Ther. 44: 579–587

Ryder, K., Glick, M. R., Opheim, K. E., Hood, L., Roullet, A., Bienvenu, J., Ou, C. N. (1983) An evaluation of the theophylline method and calibrator for the Du Pont ACA Discrete Clinical Analyzer, Du Pont Company, Willington, DE

Sarkar, M., Polk, R. E., Guzelian, P. S., Hunt, C., Karnes, H. T. (1990) In vitro effect of fluoroquinolones on theophylline metabolism. Antimicrob. Agents Chemother. 34: 594–599

Segev, S., Rehavi, M., Rubistein, E. (1988) Quinolones, theophylline and diclofenac interactions with the gamma-aminobutyric acid receptor. Antimicrob. Agents Chemother. 32: 4–6

Stone, T. W. (1982) Quinolinic acid and kynurenic acid. Trends Pharmacol. Sci. 5: 215

Tsuji, A., Sato, H., Kume, Y., Tamai, J., Okezaki, E., Nagata, O., Kato, H. (1988) Inhibitory effects of quinolone antibacterial agents on gamma-aminobutyric acid binding to receptor sites in rat brain membranes. Antimicrob. Agents Chemother. 32: 190–194

Unseld, E., Ziegler, G., Gemeinhardt, A., Janssen, U., Klotz, U. (1990) Possible interaction of fluoroquinolones with the benzodiazepine-$GABA_A$-receptor complex. Br. J. Clin. Pharmacol. 30: 63–70

Wijnands, W. J. A., Vree, T. B., Van Herwaarden, C. L. A. (1986) The influence of quinolone derivative on theophylline clearance. Br. J. Clin. Pharmacol. 22: 677–683

William, P. D., Helton, D. R. (1991) The propulsive activity of quinolone antibiotics in an animal model. Toxicol. Lett. 58: 23–28