Adverse Reactions to Fluoroquinolones. An Overview on Mechanistic Aspects

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Abstract: This review focuses on the most recent research findings on adverse reactions caused by quinolone antibiotics. Reactions of the gastrointestinal tract, the central nervous system (CNS) and the skin are the most often observed adverse effects. Occasionally major events such as phototoxicity, cardiotoxicity, arthropathy and tendinitis occur, leading to significant tolerability problems.

Over the years, several structure-activity and side-effect relationships have been developed, in an effort to improve overall antimicrobial efficacy while reducing undesirable side-effects. In this article we review the toxicity of fluoroquinolones, including the newer derivatives such levofloxacin, sparfloxacin, graepafloxacin and the 7-azabicyclo derivatives, trovafloxacin and moxifloxacin. A special attention is given to new data on mechanistic aspects, particularly those regarding CNS effects.

In recent years extensive in vivo and in vitro experiments have been performed in an attempt to explain the neurotoxic effects of quinolones sometimes observed under therapeutic conditions. However, the molecular target or receptor for such effects is still not exactly known. Several mechanisms are thought to be responsible. The involvement of γ-aminobutyric acid (GABA) and excitatory aminoacid (EAA) neurotransmission and the kinetics of quinolones distribution in brain tissue are discussed. In addition, quinolones may interact with other drugs – theophylline and nonsteroidal antinflammatory drugs (NSAID s) – in producing CNS effects.

This article provides information about the different mechanisms responsible of quinolones interaction with NSAID s, methylxanthines, warfarin and antiacids.

INTRODUCTION

Quinolones comprise a relatively large, growing and most interesting group of antibiotics which have made a major impact on the field of antimicrobial chemotherapy, particularly in the past few years. Despite some rather unpromising features of the early compounds, persistent efforts have been made over the years to produce congeners with superior antimicrobial properties, and these received considerable stimulus from the discovery that introducing fluorine into the molecule had beneficial effects [33,57].

Quinolones consist of a bicyclic ring structure (Fig. 1) in which there is a substitution at position N-1, with various moieties. All the current agents have a carboxyl group at position 3, a keto group at position 4, a fluorine atom at position 6, and a piperazinyl group or a methylpiperazinyl group at the C-7 position. Differences in the moiety present at N-1 position or at C-7 position markedly influence both microbiological and pharmacokinetic properties [107].

Generally, the 7-piperazinylated compounds have better Gram-negative than Gram-positive antimicrobial potency, whereas the converse is true for amino or aminomethylpyrrolidinyl agents. Overall, new quinolone-3-carboxylic acids having a fluorine or chlorine at position C-8 are more prevalent than their 8-H or 1,8-naphthyridine counterparts [33,109].

The mechanism of action of quinolones is through the inhibition of bacterial gyrase, an enzyme involved in DNA replication, recombination and repair [64]. By interfering with gyrase, quinolones arrest bacterial cell growth. The affinity of quinolones to metal ions seems to be an important prerequisite of their antibacterial activity: probably, quinolones bind to the DNA-gyrase-complex via a magnesium ion [74].

Compared to the early quinolones, with their poor pharmacokinetic profile and limited in vitro antimicrobial activity, the new fluorinated quinolones have much broader spectra of antibacterial activity and better pharmacokinetic profiles. In fact, they attain concentrations in most tissues and body fluids that are at least equivalent to the minimal inhibiting concentration (MIC) designated as the breakpoint for bacterial susceptibility. Thus, they have a much greater therapeutic potential than their forerunners.

Though over 10,000 chemical entities have been patented, only a very limited number of them has been approved for human use. Many have been shown to have an
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**Fig. (1).** Quinolones appearing in this review.
inappropriate spectrum of activity, others to possess a quirky pharmacokinetic profile, but the main reason for non-approval/marketing has been patient tolerability. Quinolones, in fact, are associated with side effects in approximately 5-8% of patients. Most adverse events are mild-moderate and self-limiting.

Information on the safety of drugs come from various sources, including animal experiments or clinical data. In this article we review the toxicity of fluoroquinolones, including the newer derivatives such levofloxacin, sparfloxacin, grepafloxacin and the 7-azabicyclo derivatives, such as trovafloxacin and moxifloxacin. Other compounds such as gatifloxacin, clinafloxacin, sitafloxacin and gemifloxacin are currently in development [10]. A special attention is given to new data on mechanistic aspects.

ADVERSE REACTIONS

The most common adverse experience reported for all quinolones involve the gastrointestinal tract, skin and CNS. Of the gastrointestinal events, nausea and vomiting are the most common. CNS reactions vary in severity and include dizziness, convulsions and psychoses [15,62,99]. Occasionally major events occur, which lead to significant tolerability problems. Phototoxicity, cardiotoxicity, arthropathy and tendinitis have also been observed in some patients (Table 1) [84,85,110,112].

Chemical Structure-Side Effects Relationships

Even though the precise role of specific molecular modifications in adverse events is difficult to locate, certain nuclear and side-chain configurations are associated with altered frequencies of particular adverse effects [33].

As previously described the fluoroquinolone group is based on a pharmacore nucleus with two derived molecules: quinolones and naphthyridones (Fig. 1). The former group has been more frequently manipulated to yield clinically useful agents. The naphthyridones have had a less successful history, with the recent suspension of trovafloxacin being the most notable. Prior to this event only three naphthyridones had received regulatory approval: enoxacin, tosufloxacin and trovafloxacin. All three have a chequered tolerability history.

In the quinolone family there have also been some noteworthy issues, although the two most widely used members (ciprofloxan and levofloxacin) are well tolerated. The first major issue seen with the quinolones per se was the withdrawal of temafloxacin in 1992. The precise mechanism of the "haemolytic uraemic syndrome" is still

Table 1. Severity of Adverse Effects Associated with Fluoroquinolones

<table>
<thead>
<tr>
<th>Quinolones</th>
<th>Gastrointestinal reactions</th>
<th>CNS effects</th>
<th>Phototoxicity</th>
<th>Liver toxicity</th>
<th>Hypoglycaemia</th>
<th>Tendinitis</th>
<th>Cardio toxicity</th>
<th>Haemolytic syndrome</th>
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The data from a meta-analysis of articles reported in the present manuscript are indicated. The legend indicates the severity of adverse effects: + mild, ++ moderate, +++ severe, ++++ very severe.
unclear but similar effects, such as hypoglycaemia and eosinophilia, were seen with trovafloxacin. Hepatocellular damage and other liver toxicities were also reported with trovafloxacin [10]. Both temafloxacin and trovafloxacin had a 2,4-difluorophenyl moiety at position 1 of the molecule, and appeared to initiate a significant immunological reaction. Indeed re-exposure of one patient to trovafloxacin triggered a marked hypersensitivity reaction.

Preliminary results from clinical trials suggest that moxifloxacin has a low frequency of class-related adverse events. In fact, meta-analysis of data from 20 phase II and III studies involving almost 5,000 patients indicated that adverse events were mostly mild and transient. Its most common adverse events are gastrointestinal disturbances. In contrast to some other fluoroquinolones, moxifloxacin appears to have a low propensity for causing phototoxic and CNS excitatory effects [8].

Low CNS stimulant effects were also documented for levofloxacin (the optically levorotatory isomer of ofloxacin) and temafloxacin in comparison to other fluoroquinolones [4, 58, 60]. On the contrary, among the newer drugs lomefloxacin, clinafloxacin, tosufloxacin and trovafloxacin have been reported to be the most excitatory compounds [1, 10, 86].

Quinolones have also been associated with photosensitivity or toxicity reactions [36, 94]. Quinolone phototoxicity is related to the generation of reactive oxygen species including hydrogen peroxide since these species cause severe tissue damage [108]. More phototoxic compounds tend to produce superoxide at a faster rate. Photoreactivity and thus phototoxicity are mostly influenced by the substituent in position 8 [33, 94]. Drugs that are substituted with an additional fluorene atom in this position such as fleroxacin (a trifluoro derivative) or sparfloxacin, generally exhibit a relatively high phototoxic potential, whereas quinolones without a halogen at this position such as moxifloxacin or levofloxacin, are associated with a low risk of phototoxicity [97]. High incidences of phototoxicity has been reported in man for fleroxacin, lomefloxacin, sparfloxacin and clinafloxacin [11, 39, 75, 94, 99]. For this reason, plus its potential to cause significant hypoglycaemia, clinafloxacin may find only limited application. Certain patient groups, e.g. patients with cystic fibrosis, are predisposed to this adverse effect [10].

Moreover, some quinolones have been shown to exhibit a photomutagenic and photo-carcinogenic potential which seems to increase with decreasing photostability [56, 63, 94].

Cardiotoxic potentials of sparfloxacin and grepafloxacin are higher than those of other fluoroquinolones, but during therapy no clearcut drug-related serious reactions have been reported [10, 40, 99].

Chondrotoxicity of quinolones, as observed in immature animals, can affect articular cartilage and/or the epiphyseal growth plate, depending on the developmental stage [99]. Pathogenesis of chondrotoxicity can probably be explained by magnesium-chelating properties of these drugs stage. This hypothesis is further substantiated by the fact that quinolone-induced cartilage lesion can be diminished by supplementing with magnesium and/or tocopherol [98, 99]. The safe use in children or adolescents in the growth phase, and in pregnant or lactating women has not been sufficiently documented and judging from the animal experiments, the risk of damage to the cartilage of joints in growing humans cannot altogether be excluded [96].

Another manifestation of the toxic effects of quinolones on connective tissue structure are tendopathies, as documented during pefloxacin, sparfloxacin and fleroxacin therapy [9, 10, 40]. Predisposing factors include aging, corticosteroid use, renal disease, haemodialysis and transplantation [10].

CNS Effects

CNS side effects represent the second most common group of quinolone adverse events. These effects include headache, dizziness, agitation, sleep disorders, psychoses and in rare instances convulsions [15, 35, 62].

There are several mechanisms by which quinolones may affect CNS function. These include pharmacokinetic interactions with other drugs which act on the CNS, a direct pharmacological action of the quinolone alone, and/or a pharmacodynamic interaction between quinolones and other drugs in the CNS. Interactions will be discussed in the next paragraph.

Up to now, most in vitro models and animal models were used for assessing the excitatory potential of fluoroquinolones [21-30, 86].

In an attempt to explain the underlying mechanisms the adenosine or GABA receptor has been proposed as a possible target for quinolones [32]. In addition, interactions of quinolones with dopamine, opioid and glutamergic receptors were also postulated [15].

In particular, the structural similarities of fluoroquinolones to kynurenic acid (KYNA) or other similar compounds, which are endogenous ligands of EAA receptors, might suggest an interaction of quinolones with ligand-gated glutamate receptors [100]. This is supported by the fact that the convulsive action of quinolones is antagonized by antagonists of the glutamate receptors [2, 25, 31, 86].

More frequently seizures have been roughly correlated with quinolone binding at the GABA_A receptors in the brain, thus blocking the natural ligand, GABA, leading to CNS stimulation [45, 87, 105, 106].

It is of note that a number of radioligand binding experiments indicated that certain 4-quinolones inhibit the binding of 3HGBA or 3H muscimol (MSC), a selective GABA_A receptor agonist to a crude preparation of rat or mouse brain synaptic membranes [87, 105, 106]. It should be noted that 3HMSC is a specific ligand for the GABA_A receptor by comparison with 3HGABA which may additionally bind to GABA uptake sites and GABA_B.
receptors, and hence potentially complicate the interpretation of results obtained with this ligand [1,45,87,105]. The IC$_{50}$ values (i.e. the concentration of drug required to reduce the amount of bound radioligand to 50% of control) varies widely between the quinolones with all – except norfloxacin IC$_{50}$ = 20 M – being greater than 100 M [1,32]. This concentration is at least ten times higher than would be achieved in serum with therapeutic doses.

Electrophysiological extracellular techniques as well as patch-clamp investigations were also utilized. By the voltage-clamp technique Halliwell and coworkers [43], determining the quinolone-induced functional response from single neurones maintained in vitro, demonstrated that ciprofloxacin and ofloxacin are relatively weak inhibitors of GABA-evoked currents recorded from rat dorsal root ganglion neurones. Similar results were also obtained from Akaike et al. [5] using patch clamp techniques to record from rat hippocampal neurones in vitro.

But, how selective for the GABA$_{A}$ receptor are the quinolones?

In agreement with several in vitro studies we found in animals that the epileptogenic activity of pefloxacin was suppressed by compounds enhancing GABAergic neurotransmission i.e. vigabatrin and tiagabine or by MSC and diazepam, which are agonists for the GABA$_{A}$-benzodiazepine receptor complex, while it was influenced at neurotoxic doses by baclofen (BAC), a GABA$_{B}$ receptor agonist (Fig. 2) [25,49]. However, Akahane et al. [2] demonstrated that BAC inhibited both levofloxacin and ciprofloxacin induced convulsions in mice, more effectively than the GABA$_{A}$ receptor agonists did. Thus, this study suggests that quinolones induce seizures mainly through interaction with GABA$_{B}$ receptor rather than through interaction with the GABA$_{A}$ receptor.

Additionally, there is evidence that quinolones are able to reduce the threshold of convulsions induced by pentylenetetrazol and β-lactams, both compounds which are believed to antagonize the GABA$_{A}$-benzodiazepine receptor complex [6,23,24,26,27,34,103].

From the combined data of several studies it appears that the R7 side chain substituent (Fig. 1) has the strongest influence on the degree of GABA binding inhibition [1,16,76,87,105]. Akahane et al. [1] even suggested a structural analogy between GABA and the piperazinyl and pyrrolidinyl side chains employed in most quinolones.

However, to what extent do the undoubted pharmacological effects of quinolones on the GABA$_{A}$ receptor explain the CNS adverse reactions associated with quinolone therapy? As above outlined, the effect of quinolones alone is weak, the IC$_{50}$ being 10-100 fold greater the achievable serum concentrations.

Thus, it appears questionable that a specific interaction of quinolones with GABA receptors can alone explain the convulsant activity of these compounds.

Concerning the possibility that adenosine system is involved, the potency of inhibition of the specific binding of adenosine A$_{1}$ receptor agonists L-H$^{3}$-$N^{6}$-phenylisopropyl-adenosine and H$^{3}$-$N$-ethylcarboxamidoadenosine to rat brain synaptic membranes by some quinolones does not correspond to the convulsant activity of these antibiotics and suggests that other factors must be involved [32].

![Fig. (2). GABA synapsis and sites of action of compounds enhancing GABAergic transmission. MSC is a selective GABA$_{A}$ receptor agonist, BAC is a GABA$_{B}$ receptor agonist. Benzodiazepine and phenobarbital sites are also indicated. Tiagabine is a GABA uptake inhibitor, vigabatrin is a GABA transaminase inhibitor. GAD and GABA-T are the enzymes involved in GABA synthesis and catabolism, respectively.](image-url)
On the other hand, radioligand experiments have indicated that the quinolones do not influence the binding of selective ligands to EAA, muscarinic, opioid, β-adrenergic or GABA<sub>B</sub> receptor sites [32,44,87,92].

As previously suggested, the structural similarities of fluoroquinolones to KYNA or other similar compounds which are endogenous ligands of the glutamate receptor might suggest an interaction of quinolones with ligand-gated glutamate receptors [100]. In agreement with this, recent experimental studies demonstrated that the convulsive action of quinolones is antagonized by the glutamate receptor antagonists. There is evidence that both N-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)/Kainate (KA) receptor antagonists are involved [2,25,31,86].

In our study we demonstrated that the seizures induced by pefloxacin in mice were antagonized by compounds both acting as glutamate receptor antagonists and enhancing GABA neurotransmission (Figs. 3 and 4). Concerning the anticonvulsant potencies of the different compounds tested, we found differences among the group. In particular we found that selective NMDA antagonists such as dizolcipine and 3-(±)-2-carboxypiperazin-4-ylpropenyl-1-phosphonic acid (CCPene) (Fig. 3) were able to block seizures induced by i.p. administration of pefloxacin with potencies higher than or equal to those of the GABA<sub>A</sub> agonist MSC, diazepam and the inhibitor of GABA uptake tiagabine (Fig. 2) [78,103]. In addition, we observed that compounds which are preferenzial AMPA-KA antagonists (Fig. 4), such as methylenedioxy-5H-2,3-benzodiazepine hydrochloride (GYKY 52466) and 2,3-dihydroxy-6-nitro-7-sulfamoyl-benzo(F)quinoxaline (NBQX) [13,14,25,50,71,90,104] also antagonized the seizures induced by pefloxacin, but with minor potencies compared with those of NMDA antagonists. The fact that the doses of AMPA/KA antagonists used are in the range of those which have been shown to block excitatory neurotransmission at non-NMDA receptors clearly demonstrates that AMPA/KA-dependent mechanisms are activated in the course of pefloxacin-induced seizures as well.

The broad-spectrum antagonist KYNA was also found to be a quite potent anticonvulsant with a similar trend to that of selective NMDA receptor antagonists [25].
Ifenprodil (IFE) and (±)(α)-(chlorophenyl)-4-(4-fluorophenyl)methyl)-1-piperidineethanol (SL 82.0715), two compounds acting on the polyamine site of NMDA receptor complex [11,79], were unable to protect against seizures induced by pefloxacin, suggesting that the polyamine site did not exert a principal role in the genesis of seizures induced by quinolones. Therefore, the results of our study clearly demonstrated that the excitation mediated by dicarboxylic amino acids plays a crucial role in the pathogenesis of seizures caused by pefloxacin in mice. It is most likely that excessive activation of EAA receptors occurs secondarily to or concomitantly with the impairment of the inhibitory GABAergic neurotransmission caused by pefloxacin and is essential for the propagation of seizures.

Because in our study NMDA antagonists demonstrated to be potent anticonvulsants, we think that NMDA receptors play a particularly pivotal role in quinolones induced seizures. This observation is in line with other studies showing that the proconvulsive activity of some quinolones, may be antagonized by EAA antagonists [2,111].

Therefore, we suggest to consider that quinolones besides inhibiting GABAergic transmission, might possess agonistic or modulatory properties at receptors activated by EAA_{\alpha}.

In addition we should also consider as possible mechanism the in vivo biotransformation of quinolones into chemical entities which then have the potential to interact through direct or indirect accelerating and inhibiting actions on both glutamate and GABA-benzodiazepine receptors respectively [30,111].

As above outlined, in receptor binding studies no specific affinity of quinolones for the ion- or ligand-gated glutamate receptors has been found [32,44,92].

Recently, an electrophysiological study (field potentials in the CA3 region of rat hippocampus) by Schmuck and coworkers [86] allowed an assessment of the excitatory potential of several fluoroquinolones and demonstrated a close relationship between the excitatory potency and their chemical structure. Moreover, by the extensive number of fluoroquinolones tested it was shown that all compounds dose dependently increased the population spike amplitude of the neurons. In particular, the hippocampus slice model indicated a higher excitatory potency for some newer fluoroquinolones, such as lomefloxacin, clinafloxacin, tosufloxacin and trovafloxacin. Authors suggested that the increase of the population spike amplitude could in principle be due to activation of the NMDA receptor on the CA3 region or, alternatively, to a reduction of the activity of the GABAergic inhibitory interneurons by GABA_{\alpha} antagonism. The observation that dizolcipine, a selective channel blocker of the NMDA receptor, was able to abolish the excitatory effects of clinafloxacin, strongly suggests the involvement of the NMDA channel. Dizolcipine has also been reported to antagonize the proconvulsive action of fluoroquinolones in mice [25,111]. A functional agonism to the glycine site of the NMDA receptor was also postulated for the quinolones by Dimpfel et al. [31], however, in contrast to this suggestion it was found both in binding and electrophysiological studies that fluoroquinolones did not bind to the glutamate or glycine binding site of the NMDA receptor [32,44,86,92].

Interestingly, Tanaka et al. [102] showed that fluoroquinolones decreased the blocking effects of Mg^{2+} and dizolcipine binding to the receptor channel. They, therefore, characterized the fluoroquinolones as “open channel blockers”. Considering the Mg^{2+} chelating properties of fluoroquinolones which have been also postulated as a mechanism for fluoroquinolone action in juvenile cartilage, it is tempting to speculate that the excitatory potency of fluoroquinolones might be based on activation of the NMDA receptor by abolishing the Mg^{2+} block in the ion channel [59,98]. This would prolong the opening time of the channel, thus increasing intracellular Ca^{2+} concentrations and the excitability of the neuron.

Another point that should be taken into consideration is quinolones lipophilicity, because the various degrees of proconvulsant activity exhibited by different quinolone antibiotics might be partially related to their lipophilicity. As a first approximation, one might assume that quinolones with the highest overall lipophilicity would have the greatest penetration into the CNS and brain [62]. Generally, quinolones possess a very low lipophilicity, but is possible that some quinolones as pefloxacin, which is one of the most lipophilic of the fluoroquinolones, crosses better than others the blood brain barrier [19,41]. However, in our previous study we did not demonstrate any clear correlation between lipophilicity and proconvulsant potency of quinolones [26]. In fact, in our study we found that among the classic quinolones pefloxacin showed high lipophilicity coupled with the highest proconvulsant activity (potency), but nalidixic acid, which was the most lipophilic compound, was also the least toxic. Thus, such a lack of correlation between lipophilicity and convulsant potency suggests that other factors may be responsible of the convulsant properties of quinolones rather than lipophilicity.

This induces us to consider the involvement of pharmacokinetic mechanisms so, because in vivo penetration into the brain is also an important variable.

Several investigators reported that quinolone concentrations in brain tissue and cerebrospinal fluid (CSF) are lower than in serum after systemic administration [51,83]. Recently, a number of data on the concentrations of quinolones in the brain are not widely available [28,29,45,72,73]. Thus, is still an open question whether there is any relationship between the incidence of such CNS side effects and the CNS pharmacokinetics of quinolones. These compounds differ considerably in their CSF transport and disposition. Pefloxacin exhibits a higher rate and extent of CSF transport than other quinolones, probably due to its higher lipophilicity. For this reason, it is possible that the higher proconvulsant activity induced by some compounds as pefloxacin may be related to the concentrations reached by the drug in the brain and/or to a slow clearance of the compound from the cerebral area. In fact, Sato et al. [83] reported that the transport mechanism for two quinolones, ofloxacin and lomefloxacin, across the blood-CSF barrier might involve a sequestration process from CSF into blood.
Moreover, an unidirectional efflux (sequestration) process from CSF into blood by saturable active transport has been proposed for many drugs, e.g. some β-lactam antibiotics [93,101]. Recently, Ooie and coworkers [72,73] have demonstrated that among several conventional quinolones marked differences exist in the steady state concentration ratio between CSF and brain tissue. Based on these studies, we suggest that the affinity of quinolones to a putative carrier-mediated efflux transport system may be important in reducing brain interstitial fluid concentrations and consequent CNS effects.

In the light of these evidence it must be taken into account that quinolones concentrations in the brain interstitial fluid are also determinant for the duration and severity of their CNS toxicity. According to this hypothesis, it has been recently demonstrated that this efflux transport system of quinolones from the brain can be ascribed to multiple mechanisms including P-glycoprotein and an unidentified anion-sensitive transporter operating in the brain capillary endothelial cells that constitute the blood-brain barrier [66]. However, when quinolones are administered alone there are as yet no data to show that quinolone concentrations in the human brain are anywhere near sufficient to exert clinically significant convulsant effects.

As several clinical observations indicated convulsions were almost always associated with a predisposing factor such as the elderly, severe cerebral arteriosclerosis, epilepsy, brain tumour, anoxia or alcohol abuse [15,35,62]. Otherwise, they occurred in patients receiving theophylline or the NSAID fenbufen [15,35,62]. In the light of these evidences, we performed a series of experiments to evaluate the epileptogenic properties of quinolones in genetic models of epilepsy [12,18,89]. Two particular strains of rodents, the genetically epilepsy-prone rats and Dilute Brown Agouti DBA/2J (DBA/2) mice, both genetically susceptible to sound induced seizures were used. As expected, these animals showed a much more propensity to excitatory effects of quinolones than normal ones [21-24]. We demonstrated that quinolones potentiate the convulsant effects of theophylline, ceftazolin, imipenem and pentylenetetrazole, which are well known CNS stimulant compounds [21-24,26,27].

For these reasons, quinolones are contraindicated in patients with epilepsy and must not be used in patients with preexisting CNS lesions involving a lowered convulsion threshold, e.g. after cerebrocranial injuries, inflammation in the region of CNS or stroke. It is also important to consider that even if used in accordance with the directions, quinolones may affect alertness and reaction time to such an extent that ability to drive, cross the road safely or operate machinery may be impaired [107].

**DRUG INTERACTIONS**

**Interaction with NSAIDs**

A number of potential drug interaction involving the quinolones have been reported. Probably the two most frequently referenced quinolone drug interactions are those with methylxanthine derivatives and certain NSAIDs, such as fenbufen or its metabolite 4-biphenylacetic acid (BPAA). These drug interactions are very important since they can result in considerable CNS toxicity [15,54,60,75,77,80].

As previously outlined, there is a good evidence that quinolones at high concentrations can inhibit GABA receptor binding, but when some quinolones are combined in vitro with certain NSAIDs or BPAA, their GABA receptor binding is dramatically potentiated [1,5,43,45,87,105]. While BPAA sharply enhances quinolone-induced GABA receptor inhibition, BPAA itself does not inhibit GABA receptor binding at all [3]. However the mechanism of synergistic binding inhibition of quinolones and BPAA is not fully understood [45]. Moreover, it was shown that in the presence of norfloxacin some NSAIDs suppressed the GABA response in rat hippocampal pyramidal neurons in a concentration-dependent manner [4,30]. NSAIDs differ in their potency relating to the potentation of the quinolone-induced GABA receptor inhibition [92,95].

On the basis of a molecular modeling study, it has been hypothesized that accessible cationic and anionic sites and a bulky additional binding site are necessary to allow GABA receptor antagonists [81]. As demonstrated by Akahane et al. [1], the active site in the quinolone molecule responsible for the inhibition of GABA receptor binding was, at least in part, the piperazine or amipropyrrolidine moieties at the 7 position on the parent molecule, which have structures similar to those of some GABA receptor agonists. Since the piperazine or amipropyrrolidine moieties of quinolones have a cationic nitrogen, this could be considered the cationic site of the antagonistic structure. Concerning the quinolones BPAA interaction, it has been suggested that quinolones and BPAA interact with the GABA receptor at nearby sites and that the binding affinity of quinolones to GABA receptors is largely enhanced by the intramolecular interaction with PBAA [3,52,53]. In particular, Akahane and colleagues [3] suggested that the planar heteroaromatic ring in quinolones and the biphenyl ring of BPAA may reach a parallel conformation, as to so, the secondary amine of the piperazine ring in quinolones and the carboxyl group in BPAA approach to positions close enough to enable them to produce an accessible interaction core with the GABA receptor and serve as cationic and anionic sites, respectively. These sites resemble isonicotinic acid, a GABA receptor agonist, in their interchange distance (Fig. 5).

A second hypothesis suggests the existence of a novel binding site for the NSAID on the GABA receptor complex [95]. According to this suggestion, quinolones could bind to their own site and, this interaction would hinder the association of BPAA to other sites on or around the receptor. In particular, Squires and Saederup [95] suggested that piperazinequinolones like norfloxacin, acting at GABA receptors, induce a high affinity binding site for BPAA-like NSAID that when occupied, reciprocally increases the affinities of the quinolones for GABA receptors. This site is postulated to be a new site on the GABA receptor complex.
In addition, it has been suggested that the molecular properties of GABA_A receptor complex in different regions of the CNS may influence the interaction of NSAID with quinolones at GABA_A receptors [65,42].

Concerning the chemical structure-activity relationship, quinolones with unsubstituted piperazine show a strong NSAID interaction, while those with C-alkilated piperazines (bulky) and the pyrrolidines have minimal effects (Fig. 1). There is no significant relationship with any of the other quinolone substituents R_1, R_5, or X_8 [33].

In vitro studies also demonstrated that ciprofloxacin and BPAA have no effect at ionotropic glutamate, serotonergic

Fig. (5). Presumed conformation of the hypothetical quinolone-BPAA hybrid molecule at the GABA_A receptor site. Cationic and anionic sites approach to positions close enough to enable them to produce the interaction core with the GABA_A receptor. These sites resemble isonipecotic acid (a GABA receptor agonist) in their interchange distance.
Though combinations of quinolones and BPAA do not seem directly interact with the glutamate receptor biochemically or electrophysiologically, intrathecal injection of glutamate antagonists rather than GABA agonists protects mice against convulsions elicited by combination of quinolones and BPAA [2,32,92].

Using convulsions as endpoints, few in vivo studies have been performed. Following the concomitant administration of fenbufen and some quinolones seizures were observed in rats and mice. In particular, it has been reported that differences exist among different quinolones with respect to the lowest effective dose and to the lag time until seizures occurred [1,2,15,111].

A possible pharmacokinetic mechanism between quinolones and fenbufen was also investigated in experimental animals. A number of studies demonstrated that serum concentrations of norfloxacin and ofloxacin were significantly elevated by coadministration with fenbufen [67,68]. It has also demonstrated that fenbufen facilitated the entry of ciprofloxacin, norfloxacin and ofloxacin into the CNS, thus elevating the concentrations of these quinolones in the brain and CSF [51,69]. However, in a study based on the similar experimental model any pharmacokinetic interaction has been demonstrated between fenbufen and sparfloxacin [70].

**Interaction with Methylxanthines**

In several studies, patients receiving theophylline and some quinolones concomitantly developed CNS side effects, including convulsions [35,54,60]. A pharmacokinetic mechanism which involves the inhibition of the cytochrome P450IA2 enzymes responsible for metabolism of methylxanthines has been suggested [37,38]. Concomitant administration of quinolones and theophylline may, thus, prolong the half-life of theophylline, elevate serum theophylline concentrations, and increase the risk of theophylline-related adverse events [108]. The level of quinolone-theophylline interactions has been monitored in in vivo at the enzyme level [37,38,82] or in animals and man at the pharmacokinetic level [47,48,54]. In particular, it has been described that the extent of inhibition by quinolones depends not only on the affinity of a quinolone to the site but also on the concentration of this drug and possible active metabolite at the cytochrome binding site [37]. Numerous quinolones were examined to determine which structural features contribute most to cytochrome P450IA2 inhibition [33,37,38,47].

In particular, it has been suggested by Domagala [33] that the theophylline-quinolone interaction is controlled primarily by the nature of the R7 side chain, but is also influenced by the R8 substituent and to a lesser extent by X8 as well (Fig. 1). The highest interactions occur for small non-bulky substituents such as piperazines, pyrrolidines, and even non-ring side chains. Even R7 groups as small as methyl or fluoro show high interactions. The R1 substituent is less important than R7. It also appears that bulkier X8 substituents are preferred with naphthyridines (X8 = N) the least preferred.

However, Ball [9] reported epileptic activity in patients who received both quinolones and theophylline, but not displaying elevated theophylline plasma levels.

In the light of this evidence, thus, we suggest to consider, besides the pharmacokinetic mechanism, also a pharmacodynamic interaction which results in a pronounced enhancement of CNS convulsant properties of both quinolones and theophylline.

As it is well known, GABA and EAA play a primary role in various seizure model, included seizures induced by quinolone antibiotics and xanthine derivatives [17,32,87]. In an attempt to better investigate this interaction, we performed a series of experiments in animals [21,22].

In these studies we demonstrated marked differences among quinolones to potentiate the convulsant properties of theophylline in rats providing a further evidence that some quinolones possess proconvulsant activity as previously described in man.

The proconvulsant properties of quinolones were also observed in mice administered with cefazolin or imipenem [23,24]. Like theophylline and quinolones, also β-lactams possess epileptogenic properties, which have been attributed to the inhibition of GABA system [6,20]. Thus, it appears quite probable that quinolones may potentiate the epileptogenic activities of β-lactams so.

**Interaction with Warfarin**

Some quinolones (e.g., norfloxacin or ofloxacin) have been reported to enhance the effects of the oral anticoagulant warfarin or its derivatives. However it is suggested that a warfarin-quinolone interaction occurs only at higher doses of the antibacterial agent [107].

**Interaction with Antiacids**

Gastrointestinal absorption of all oral quinolones is reduced by concomitant administration of magnesium- or aluminium-containing antiacids and with calcium, iron and zinc. The decrease in absorption may be as much as 70 fold and may lead to treatment failure [61]. The event depends on the fact that quinolones chelate with several polyvalent cations, such as Ca^{2+}, Mg^{2+} and Fe^{2+} among others [55]. Since the chelation of the quinolone to the metal ion occurs through the C3 and C4 dicarbonyls the interaction with metal ions is common to all quinolones [91].

**CONCLUSIONS**

In this review, we have attempted to provide information about the toxicity of fluoroquinolones, focusing special attention on new data on mechanistic aspects. The data

(5-HT3), nicotinic, purinergic (P2) and strychnine-sensitive glycine receptors [42,46].
presented here arise from work around the world as part of clinical trials and postmarketing surveillance studies. The safety profile are comparable for all quinolones, although there are differences in both the incidence and the type of reactions induced by certain compounds. In many cases, fluoroquinolone adverse events are dose- and structure-related. Therefore, understanding the structure-toxicity relationships may allow design of future compounds free of such effects.

**ABBREVIATIONS**

- **AMP** = α-Amino-3-hydroxy-5-methyl-4-isoxazolepro-pionic acid
- **BAC** = Baclofen, a GABA<sub>B</sub> receptor agonist
- **BPAA** = 4-Biphenylacetic acid
- **CA<sub>1</sub>** = Region of hippocampus
- **CCPene** = 3-(±)-2-Carboxypiperazin-4-ylpropenyl-1-phosphonic acid, a competitive NMDA receptor antagonist
- **CSF** = Cerebrospinal Fluid
- **CNS** = Central Nervous System
- **DBA/2** = Dilute Brown Agouti DBA/2J
- **EEA** = Excitatory aminoacid
- **GABA** = γ-Aminobutyric acid
- **GAD** = Glutamic acid decarboxylase
- **GABA-T** = GABA transaminase
- **GIKY 52466** = Methyleneoxy-5H-2,3-benzodiazepine, an AMPA/KA receptor antagonist
- **5-HT<sub>3</sub>** = Subtype of serotonin receptor
- **IC<sub>50</sub>** = Concentration of drug required to reduce the amount of bound radioligand to 50% of control
- **IFE** = (±)(E)-2-Amino-4-methyl-5-phosphono-3-pentenoate ethyl ester o Ifenprodil, a competitive NMDA receptor antagonist
- **KA** = Kainate
- **KYNA** = Kynurenic acid, a Broad-spectrum EAA antagonist
- **MIC** = Minimal inhibiting concentration
- **MSC** = Muscimol, a selective GABA<sub>A</sub> receptor agonist
- **NBQX** = 2,3-Dihydroxy-6-nitro-7-sulfamoyl-benzo(F)-quinoxaline, an AMPA/KA receptor antagonist
- **NMDA** = N-Methyl-D-aspartate
- **NSAID<sub>3</sub>** = Non steroidal anti-inflammatory drugs
- **P<sub>2</sub>** = Subtype of purinergic receptor
- **SL 82.0715** = (±)(a)-(Chlorophenyl)-4-(4-fluorophenyl)methyl)-1-piperidineethanol, a non competitive NMDA receptor antagonist

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Adverse Reactions to Fluoroquinolones

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