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# Toxicity of Quinolones

*Ralf Stahlmann*[1] and *Hartmut Lode*[2]

1 Institute of Clinical Pharmacology and Toxicology, Department of Toxicology, University Medical Center Benjamin Franklin, Freie Universität Berlin, Berlin, Germany
2 Hospital Zehlendorf, Heckeshorn, Department of Chest and Infectious Diseases, afil. Freie Universität Berlin, Berlin, Germany

## Abstract

Reactions of the gastrointestinal tract, the CNS and the skin are the most often observed adverse effects during therapy with fluoroquinolones. At least for some of the newer fluoroquinolones a steep dose-response relationship of adverse effects seems to exist. Pathogenesis of the neurotoxic effects of fluoroquinolones is still unknown. Among the newer drugs, trovafloxacin caused mild CNS reactions such as dizziness and lightheadedness in a considerable proportion of patients. Young females seem to be especially sensitive to this effect, which diminishes during treatment or if taken together with food. 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, apart from a slight prolongation of the QT interval. However, to avoid risks these drugs should not be prescribed to patients with known prolongation of the QT interval (e.g. patients on antiarrhythmics).

Phototoxicity has been described for all quinolones, but derivatives with a halogen atom at position 8 show the highest potential for such reactions. Fleroxacin, sparfloxacin, clinafloxacin and lomefloxacin belong to this group of fluoroquinolones. The phototoxic potential of the other new fluoroquinolones is considerably lower, but extensive exposure to UV light should generally be avoided during therapy with all quinolones.

Chondrotoxicity of quinolones, as observed in immature animals, can affect articular cartilage and/or the epiphyseal growth plate, depending on the developmental stage. Pathogenesis of chondrotoxicity can probably be explained by the magnesium-chelating properties of these drugs. As juveniles are especially sensitive, use of these drugs in paediatrics should be restricted to carefully selected indications (such as the use of ciprofloxacin in cystic fibrosis).

Another manifestation of the toxic effects of quinolones on connective tissue structures are tendopathies. Tendinitis and tendon ruptures have occurred as late as several months after quinolone treatment.

Overall, quinolones are well tolerated drugs. Their specific toxic potentials have to be considered when they are chosen for treatment of bacterial infections.

Information on the safety of drugs comes from various sources, including animal experiments or clinical data, which have their specific advantages and disadvantages. One of the most important questions in addressing drug safety information regards the precise differences between various drugs of a single class. As a general rule, statements on such differences should derive from comparative, double-blind studies only. Such studies will be quoted in this overview as far as they are available and as far as they indicate significant differences between the drugs. Overall, fluoroquinolones are relatively safe and well tolerated drugs; results of most double-blind studies have shown no significant differences between quinolones and other antimicrobials.[1]

In this article we briefly review the toxicity of fluoroquinolones, focusing special attention on the newer derivatives such as levofloxacin (which is the L-enantiomer of ofloxacin), sparfloxacin, grepafloxacin, trovafloxacin and moxifloxacin, with increased activity against Gram-positive bacteria. Special attention is given to new data on mechanistic

aspects, for example those data that indicate a link between the magnesium-chelating properties of the drugs and their adverse reactions.

It is a common feature of all quinolones that they form chelate complexes with di- and trivalent cations. The following order of stability constants for fluoroquinolones with divalent metal cations in aqueous solutions has been reported: $Cu^{2+} > Fe^{2+} > Zn^{2+} > Mg^{2+} > Ca^{2+}$.[2] 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.[3] The metal binding of fluoroquinolones has been discussed extensively in the context of the reduced bioavailability of fluoroquinolones after concomitant intake with mineral antacids or other metal-containing drugs. For details on this aspect the reader is referred to the literature.[1,4,5] Experimental data indicate that the chondrotoxicity of quinolones is related to the magnesium-chelating properties of the drugs (see section 5). It is tempting to speculate that the magnesium antagonistic effects of quinolones also induce, or at least partly contribute to, the neurotoxicity or the cardiotoxicity of fluoroquinolones.[6] This may offer the possibility of preventing these effects by treatment with magnesium.

More comprehensive reviews on quinolone-induced toxicity have been published previously by ourselves and others.[1,7-11]

## 1. Effects on the Gastrointestinal Tract

The most common adverse reactions reported during therapy with fluoroquinolones are gastrointestinal symptoms, as is commonly reported after treatment with other antimicrobials. Nausea, vomiting, abdominal pain, diarrhoea and other symptoms have been observed with all fluoroquinolones, but differences exist with respect to the frequencies of these effects. Based on the data available so far, some of the newer fluoroquinolones (e.g. grepafloxacin), in particular at higher doses, cause gastrointestinal tract reactions more often than the older drugs, ciprofloxacin or ofloxacin.[11]

Nausea, for example, was observed in 8, 11, or 15% of patients treated with grepafloxacin 200, 400 or 600mg (comparators: 8%).[10] In double-blind comparative trials with grepafloxacin at 2 doses (400 or 600mg once daily) in patients with acute exacerbations of chronic bronchitis, tolerability at the lower dose was similar to that of amoxicillin 500mg 3 times daily; however, adverse reactions at the higher dose were significantly more frequent than with the β-lactam antibiotic.[12] Results from another double-blind study, comparing grepafloxacin and ciprofloxacin, were similar: nausea was reported in 13% (ciprofloxacin 500mg twice daily), 15% (grepafloxacin 400mg once daily) and 22% (grepafloxacin 600mg once daily) of patients. The difference in the incidence of this adverse effect between high dose grepafloxacin and ciprofloxacin was statistically significant.[13]

Comparative studies with moxifloxacin have not been published to date, but an analysis of the data from 20 phase II and phase III trials (approximately 5000 patients, mostly treated with moxifloxacin 400mg once daily) revealed that nausea occurred in 7.8% of patients (all comparators: 5.7%). The discontinuation rate due to this adverse effect was 0.8%.[14]

## 2. CNS Effects

Adverse reactions of the CNS are a well-known complication during therapy with quinolones. Mild neurotoxic reactions of the fluoroquinolones include headache, dizziness, tiredness, sleeplessness, abnormal vision, restlessness, and bad dreams. Severe neurotoxic effects (psychotic reactions, hallucinations, depression and convulsions) are rare (<0.5%). The dose-dependency of CNS-stimulatory effects have been shown with fleroxacin and other fluoroquinolones. In an early double-blind evaluation of fleroxacin, using 400, 600 and 800mg once daily for 7 days in the treatment of uncomplicated genital infections, severe insomnia was seen in 8% of patients treated with 400mg daily, but in approximately 60% of patients (16/26) receiving the once-daily 800mg regimen, which is not licensed or recommended for therapy.[15]

During treatment with trovafloxacin, CNS symptoms such as dizziness and lightheadedness have been observed at variable frequencies. In some reports the incidences were >10% of the patients. Usually, symptoms resolved with continued administration. Recent data have shown that such effects have occurred more frequently in females than in males and were more frequent in individuals aged ≤45 years. A large placebo-controlled, double-blind study in 169 healthy, young females (mean age, 24.7 years) showed that the incidence of dizziness/lightheadedness in this population can be significantly reduced by administering with food, with an additional reduction associated with bedtime administration.[16]

In approximately 4 to 5% of patients treated with grepafloxacin, dizziness was noted as an adverse event.[10] With moxifloxacin, dizziness was reported in 2.8% of patients with a discontinuation rate of 0.5% due to this adverse reaction.[14] A strict comparison of the results is not justified because they do not derive from direct comparative studies.

To date the mechanism of CNS toxicity of quinolones is unknown. Extensive toxicological and biochemical experiments have been performed in an attempt to explain the CNS effects observed under therapeutic conditions. However, the molecular target or receptor for the effects of the quinolones on the CNS is still not exactly known. Some studies indicate that quinolones inhibit receptor binding of gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter. However, it seems doubtful that an interaction with GABA receptors could explain the adverse experiences during therapy with quinolones. Convulsive seizures can be induced in mice by concomitant administration of fenbufen and fluoroquinolones. The *in vitro* GABA antagonistic effects of quinolones depend on the substituent at position 7 of the heterocyclic moiety. Derivatives with a free piperazinyl group show stronger activities in such assays compared with quinolones with a methylated piperazine ring. However, the effects of quinolones on the binding of $^{[3H]}$GABA to its receptor are weak and cannot explain their epileptogenic properties. In the presence of fenbufen or its main metabolite, biphenyl acetic acid, the inhibitory effect of quinolones on GABA binding is enhanced.[9,17,18] None of the newer fluoroquinolones discussed in this paper induced convulsions in mice when administered in conjunction with fenbufen, although it should be kept in mind that experimental conditions varied in these experiments which were not always conducted in a direct comparative fashion.[1,10,11,19]

As receptor binding studies have so far failed to predict the convulsive potency of the different fluoroquinolones, the hippocampus slice model was used for studying the neurotoxic effects of a series of fluoroquinolones.[20] The electrophysiological determination of the field potentials in the CA1 region of the rat hippocampus slice allowed an assessment of the excitatory potential of fluoroquinolones. Drugs were investigated at concentrations that were comparable to therapeutic concentrations in the brain. All compounds increased the population spike amplitude in a concentration-dependent manner. Ofloxacin, ciprofloxacin and moxifloxacin were among those that increased the population spike amplitude only moderately, whereas trovafloxacin, clinafloxacin and some investigational compounds were much more excitatory. This *in vitro* system allows one to investigate the effects of the drugs at varying cation concentrations. Slight changes in magnesium concentrations led to a strong amplification of the effects. For example, clinafloxacin (2 μmol/L) induced an increase in the population spike amplitude of 233% at physiological $Mg^{++}$ concentrations of 2 mmol/L. A slight decrease in $Mg^{++}$ concentrations (1.75 mmol/L) potentiated very strongly the clinafloxacin effect.[20] Blocking the ion channel of the NMDA receptor by the antagonist MK-801 counteracts the effects of quinolones in a concentration-dependent manner, thus pointing to a direct involvement of the NMDA-gated ion channel in the excitatory effects of fluoroquinolones. It is of further interest that seizures induced either by quinolones or by magnesium deficiency can be antagonised by MK-801.[21,22]

## 3. Cardiotoxicity

Preclinical toxicological evaluation of fluoroquinolones in animals showed that they can induce cardiovascular effects such as hypotension or tachycardia after intravenous injection. Some effects might be induced via histamine release (which is also observed in animals during dietary-induced magnesium deficiency). In addition, quinolones have the potential to directly alter cardiac rhythm. Such data derive, for example, from experimental studies with sparfloxacin and grepafloxacin after oral or, in particular, after intravenous injection (both drugs are not available for intravenous treatment). It should be mentioned in this context that prolongation of the QT interval and cardiac arrhythmias, such as torsade de pointes, are known clinical manifestations of hypomagnesaemia.[23]

After long term oral treatment with sparfloxacin 25mg, prolongation of the QT interval was observed in dogs.[24] The cardiovascular effects of grepafloxacin have been compared with those of ciprofloxacin after intravenous treatment in the anaesthetised rabbit. Grepafloxacin caused transient dysrhythmias in 1/4 (10 mg/kg) and 4/4 animals (30 mg/kg). At 30 mg/kg, one animal developed ventricular tachycardia. Ciprofloxacin did not produce any changes in cardiac rhythm at this dose level, but after a 10 times higher dose (300 mg/kg) ventricular tachycardia was also observed with ciprofloxacin or lomefloxacin.[10]

Careful evaluation of clinical data showed that a small number of patients treated with sparfloxacin experienced a QTc interval prolongation to >500 msec, which might be of clinical significance. Therefore, it has been recommended that coadministration of sparfloxacin with other drugs known to increase the QT interval, or to induce bradycardia, should be avoided. Similarly, grepafloxacin caused a slight prolongation of the QTc intervals in clinical trials and presently it is not recommended for use in patients with ongoing proarrhythmic conditions. So far, significant alterations of the QTc interval have not been observed in clinical trials with levofloxacin, trovafloxacin or moxifloxacin.

## 4. Skin Reactions, Phototoxicity

The incidence of cutaneous hypersensitivity reactions (including erythema, pruritus, urticaria and rash) reported after quinolone treatment is low (<1%). Phototoxicity has been observed with all quinolones known so far and this adverse effect has gained special attention because there are significant differences between the individual drugs. Clinical manifestations range from mild erythema to severe bullous eruptions at the sun-exposed skin areas. Preclinically, it can be estimated by measuring the rates of degradation of the compounds when exposed to UVA radiation, by measuring cellular damage *in vitro* or by using *in vivo* models. The most phototoxic quinolones are those that induce singlet oxygen and radicals, since these species cause severe tissue damage. Photoreactivity and thus phototoxicity are mostly influenced by the substituent in position 8.[25] Drugs that are substituted with an additional fluorine atom in this position, such as fleroxacin, lomefloxacin or sparfloxacin, generally exhibit a relatively high phototoxic potential, whereas a methoxy group in this position (as in moxifloxacin) confers photostability. Newer fluoroquinolones, which have been developed after these structure-activity relationships were recognised, such as grepafloxacin, trovafloxacin or moxifloxacin, exhibit only a low potential for phototoxicity.[10,19]

Some quinolones have been shown to exhibit a photomutagenic and photocarcinogenic potential which seems to increase with decreasing photostability. Tumour development was noticed in animals chronically exposed to fluoroquinolones (up to 78 weeks) and UVA light. Except for those animals treated with lomefloxacin, almost all of the skin tumours were of the benign type. The implications for humans undergoing short term antibacterial therapy remain unclear, but a consequent prevention of exposure to sunlight or artificial UVA sources during treatment with quinolones is strongly recommended.[1,9]

## 5. Chondrotoxicity

Quinolones exhibit toxic effects on the immature joint cartilage (epiphyseal-articular complex) in all animal species studied. Adult articular cartilage does not react correspondingly, or at least is much less sensitive. Doses needed to induce cartilage damage in juvenile dogs are in the range of therapeutically used doses and, therefore, these drugs are contraindicated in paediatric patients. This decision has induced some controversies and several arguments have been raised against the restricted paediatric use of valuable antimicrobial agents.

Some of the most often raised issues addressing this effect shall briefly be discussed here:

### 5.1 Doses Needed to Induce Chondrotoxicity in Rodents are Much Higher than Therapeutic Doses

It must be considered that kinetics differ considerably between species. Therefore, it is not justified to compare doses across species without considering the concentrations achieved in animals and humans. Recent data also show that, in juvenile rats, cartilage lesions can be observed at doses leading to plasma concentrations in the range of relevant concentrations in humans.[26]

### 5.2 Irreversibility

Several studies in animals of various species have shown that although the clinical symptoms observed show reversibility (e.g. gait alterations), the histological changes are not completely reversible.[27] It is not known whether early alterations of joint cartilage can be reversible in animals. For any risk assessment it should at least be considered that the occurrence of clinical symptoms and the induction of tissue defects can show some discrepancy.

### 5.3 Effects on the Epiphyseal Growth Plate

Of special concern is the fact that quinolones in newborn or very young animals also affect the epiphyseal growth plate (in addition to the articular-epiphyseal complex). Very young animals have not been studied extensively, but some systematic data with trovafloxacin in newborn rats indicate that this compound (and probably other quinolones as well) can induce such changes that are associated with an interruption of the normal growth of the long bones in rats. Peak plasma concentrations of the fluoroquinolone measured in these animals under the conditions of the study were 11.3 mg/L, thus approximately 3 times higher than in humans during therapy.[1] Changes in the epiphyseal growth plate have also been observed with moxifloxacin in immature dogs aged 10 to 12 weeks, but not in dogs aged 18 to 22 weeks.[19] It is probable that such defects can be induced with all quinolones in very young animals, and further studies are needed to elucidate the phase-specificity of these effects.

### 5.4 Severe Chondrotoxicity Has Not Been Observed after the Use of Quinolones in Children

It should not be overlooked that by far the most human data derive from experience with 3 compounds: nalidixic acid, norfloxacin and ciprofloxacin.[28] A common feature of these quinolones is that they have poor tissue penetration (nalidixic acid) or lead to a comparatively low systemic exposure (the AUCs calculated for norfloxacin and ciprofloxacin are significantly lower than those for other quinolones). Drugs such as pefloxacin, which lead to 5 to 10 times higher systemic exposure (higher AUCs), are well known to be associated with a high incidence of arthropathy in humans.[29] In other words, it is not justified to generalise from the experience with one quinolone to the whole class of compounds. Although chondrotoxicity is considered a class effect, considerable differences seem to exist with respect to the risks associated with individual quinolones.[1,30]

### 5.5 Mechanism of Quinolone-Induced Chondrotoxicity

Early data from the 1950s showed that in juvenile dogs fed a magnesium-deficient diet, gait alterations were described that closely resemble those observed after quinolone treatment.[31] In rats, joint cartilage lesions observed after feeding a magnesium-deficient diet for 9 days or longer, could not be distinguished from lesions induced by quinolones.[32] From these findings it can be assumed that chelation of magnesium in joint cartilage is probably the crucial event leading to subsequent reactions, including radical formation[33] that can finally induce irreversible cartilage lesions. This hypothesis is further substantiated by the fact that quinolone-induced cartilage lesion can be diminished by supplementing with magnesium and/or tocopherol.[34]

## 6. Tendon Disorders (Tendinitis, Tendon Ruptures)

In 1991, the first detailed description of fluoroquinolone-associated tendon ruptures were reported. With the increasing knowledge of this fluoroquinolone adverse effect, nearly 1000 cases of fluoroquinolone-induced tendinitis had been reported to the French drug surveillance agency up to 1997. With regard to the clinical manifestations of this adverse reaction, several phases can be distinguished: congestive and/or inflammatory oedema is the earliest sign and can mimic venous thrombosis. The tendon then becomes painful and swollen and, in 50% of all cases, is bilateral. Failure to take appropriate therapeutic measures at this stage may lead to tendon rupture. The manifestations persist for several weeks or months and result in significant functional impairment.[35]

Compared with the data reported from France, far fewer data on this adverse effect come from other countries. Pefloxacin is the fluoroquinolone most often associated with cases of tendinitis; the fact that this drug is mainly marketed in France could explain some of the geographic disparities, but under-reporting seems to be an even more important aspect.

In a compilation of more than 400 cases within an 18-month period, it was shown that treatment with ofloxacin, norfloxacin and ciprofloxacin in addition to pefloxacin – was associated with tendinitis and tendon ruptures. Most patients (70%) were aged ≥60 years. A minority (10%) of the patients with tendinitis had also received corticosteroid treatment, which is known to be associated with adverse effects on the tendons. Of major concern is the fact that the time between the beginning of treatment and onset of tendinitis symptoms ranged from 1 to 152 days. Achilles tendon ruptures have been reported to occur for as long as 120 days after the start of treatment and can occur even after drug withdrawal.[36]

Recent data have shown that ultrastructural alterations in tendocytes are observable in juvenile and adult rats after treatment with ofloxacin. Effects were more pronounced when the animals were simultaneously given a magnesium-deficient diet, suggesting that the pathophysiology of tendopathy resembles that of arthropathy.[37]

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Correspondence and reprints: Prof. Dr *Ralf Stahlmann*, Institute of Clinical Pharmacology and Toxicology, Department of Toxicology, Benjamin Franklin Medical Center, Freie Universität Berlin, Garystrasse 5, D-14195 Berlin, Germany.