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SESSION 12

Specific Toxicologic Aspects of the Quinolones

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Possible targets of quinolone toxicity include the juvenile joint, the kidney, the central nervous system (CNS), the eye, and the cardiovascular system. In immature animals all quinolones studied cause arthropathies of the major diarthrodial joints. Arthropathies have also developed in adult dogs after 12 months of pefloxacin treatment. At high doses the quinolones exert effects on renal function that are related to a foreign-body reaction caused by crystals; nephropathologic changes seem not to occur without crystalluria. In humans quinolones can have various CNS effects. The subcellular "substrate" for these effects is unknown. Further understanding of severe CNS reactions (confusion, hallucination, anxiety, agitation, nightmares, convulsive seizures, and depression) is needed. Pefloxacin causes cataracts in dogs after treatment for 8–12 months. Low-dose quinolones (administered as an intravenous bolus) cause pronounced but transient systolic hypotension in dogs and cats; cardiovascular effects may be mediated by histamine release. Quinolones inhibit the bacterial enzyme DNA gyrase. To exclude the possibility of damage to mammalian DNA, mutagenicity studies have been performed. Since all but two tests (which may give false-positive results) have been negative, quinolones appear to be nonmutagenic. Photosensitivity has occurred in humans given quinolones. Drug interactions can be clinically important.

The new quinolones, including norfloxacin, ofloxacin, ciprofloxacin, enoxacin, and pefloxacin, have proven to be valuable drugs with interesting microbiologic, pharmacokinetic, and therapeutic properties [1–9]. Related compounds—e.g., fleroxacin (Ro 23-6240), amifloxacin, difloxacin, and NY-198—are currently undergoing clinical investigation.

All of these compounds contain a piperazine moiety and at least one fluorine atom. Their efficacy against *Pseudomonas* seems to be associated with the piperazine ring, which is also present in several β-lactam antibiotics with antipseudomonal activity (e.g., piperacillin and cefoperazone).

Norfloxacin was introduced to the German market at the end of 1983, ofloxacin in June 1985, and both ciprofloxacin and enoxacin in early 1987. Until now pefloxacin has been registered only in France.

Urinary tract infections, gonorrhea, and bacterial enteritis have emerged as major targets of the fluorinated quinolones. With their broad spectrum of antibacterial activity and their good distribution in most tissues and body fluids, the newer quinolones (ofloxacin, ciprofloxacin, enoxacin, pefloxacin) can be used in many types of infection, including respiratory tract infection, typhoid fever, shigellosis, otitis media (especially that caused by gram-negative bacteria in adults), soft tissue infection, and osteomyelitis. The more active quinolones for which there is an intravenous formulation (ciprofloxacin, pefloxacin) are also suitable for the treatment of severe systemic infections. In clinical trials, ofloxacin and ciprofloxacin have been effective against infections caused by *Mycobacterium* species (e.g., tuberculosis) [2, 4].

The toxicity of the new quinolones in preclinical studies and the ability of humans to tolerate these drugs are the topics of this paper. Some toxic effects have so far been observed only in animals; the meaning of these findings for humans remains unclear. The fluorinated quinolones are well tolerated by humans. Only rarely have severe adverse reactions led to the discontinuation of treatment.

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Toxicity of the Quinolones

The published toxicologic profile for the quinolones includes arthropathy, nephropathy, CNS effects, ocu-

lar toxicity, impairment of spermatogenesis, metabolic drug interactions, cardiovascular effects, possible mutagenicity, and photosensitivity. Problems involved in the clinical use of quinolones are summarized in table 1.

Table 1. Problems arising from quinolone therapy.

Problem	Implication(s) for clinical use
Arthropathies in young animals	Contraindicated for nursing mothers, children, and adolescents; caution required regarding use in patients with cystic fibrosis or life-threatening infections
	Contraindicated for pregnant women
CNS toxicity (e.g., seizures, depression)	Special benefit/risk evaluation for patients at risk
Nephropathy in animals	Dose reduction for patients with impaired renal function
Adverse reactions to long-term treatment (arthropathies and ocular toxicity in adult dogs)	Periodic ophthalmologic examinations; long-term observation of patients to detect arthropathies

Arthropathy

When administered to immature animals (rats, rabbits, dogs), all of the quinolones studied cause lesions in the cartilage of the major diarthrodial joints [10–15]. Dogs are much more sensitive than rats to these agents. The younger the animal, the worse the lesions and the shorter the interval between drug administration and lesion development.

With ofloxacin and ciprofloxacin, a variety of alterations are dose dependent but occur at different doses in different species. For example, damage to the weight-bearing joints occurred in 3- to 4-month-old dogs given 7–28 days of oral treatment with 20 mg of ofloxacin/(kg·d) or 30 mg of ciprofloxacin/(kg·d). In 4- to 5-week-old rats, however, the doses required for the production of similar effects were 100–300 and 500 mg/(kg·d), respectively for 7–10 days.

Although nalidixic acid is known to cause extensive damage to cartilage in young animals, no such adverse reactions to the clinical use of this drug have been reported, despite frequent administration to children.

Thus, species differences may be an important factor in articular damage. The clarification of this issue is expected to require epidemiologic studies over a period of 20–40 years.

Arthropathies have also been detected in adult dogs after 12 months of oral treatment with pefloxacin (140 mg/(kg·d). Results of similar long-term studies with other quinolones are not yet available.

On the basis of early investigations with pipemidic acid, it was assumed that joint damage would involve only those joints subjected to static stress during therapy. Subsequent studies, however, have shown that lesions can develop in immobilized joints, although to a less severe degree.

The pathogenesis and/or biochemical mechanism involved at the molecular level in the development of arthropathies are still unknown. Morphologic findings include erosions in joint cartilage accompanied by a noninflammatory and cell-free effusion in the joint cavity. This situation results in a reduction in the quality of the cartilage or in degeneration. Cartilage affected by lesions is usually incapable of regeneration; therefore, these lesions not only are a source of poor cartilage quality but also serve as the starting point for arthropathia deformans. In the most severely stressed sites of the joint cartilage, further erosion takes place. The soluble decomposition products of the cartilage may cause an additional irritative reaction of the synovia in the form of an effusion (i.e., synovitis serosa). This primary form of arthropathia deformans occurs in both animals and humans and may result in chronic arthrosis deformans (rheumatoid arthritis).

Nephropathy

The quinolones probably are not primarily nephrotoxic. At high doses their effects on renal function are related to a foreign-body reaction caused by crystals. The nephrotoxic potential of the quinolones in rats, monkeys, and dogs differs widely. Potential changes include mild interstitial nephritis, crystalluria, occult blood in urine, decreased renal function, and increased renal weight [15, 16]. Renal tolerance of the quinolones is linked to the pH-dependent solubility of the compounds, with minimal values at pH 6–9.

Even quinolone doses that induce a distinct crystalluria do not necessarily give rise to renal damage. Nephropathologic changes do not seem to occur in the absence of crystalluria. The doses needed to pro-

duce nephropathologic changes vary greatly with the specific quinolone and the animal species involved. In rats the necessary dose ranges from 20–30 mg/kg iv to 500–1,000 mg/kg orally. In dogs oral doses as low as 50–100 mg/kg can cause nephropathies. When the quinolones are administered by infusion, the safety margin seems to be greater than that with bolus injection.

Crystalluria in animals appears to occur under urinary pH conditions that do not generally exist in humans; specifically, alkaline pH prevails in the urine of rats and monkeys. The fact that drug-related crystalluria has been observed only rarely in humans during the clinical investigation of the quinolones seems to support this hypothesis. Nevertheless, patients receiving quinolones (especially high-dose ciprofloxacin) should be well hydrated, and alkalinity of the urine should be avoided.

CNS Toxicity

In humans, the quinolones can cause various CNS reactions, including seizures, depression, anxiety, euphoria, somnolence, and insomnia [1, 4, 16, 17]. In animals, only minimal effects on general behavior, locomotor activity, and rotarod performance have been seen. In mice, convulsions can be produced only by the administration of fleroxacin (800 mg/kg orally); the same dose of ofloxacin, enoxacin, ciprofloxacin, pefloxacin, or norfloxacin does not produce convulsions (W. Christ, K. Gindler, M. Jacobsen, W. Hecker, and H. Junge, unpublished observations). An "abnormal" electroencephalogram was observed in cats and dogs (but not in rats or monkeys) only after intravenous injection (dose, ≥25 mg/kg). The subcellular "substrate" or receptor for the effects of the quinolones on the CNS is unknown; several investigators are studying the interaction of quinolones with the GABA receptor.

Ocular Toxicity

Opthalmic toxicity of quinolones has been noted in some animals. Rosoxacin has been shown to cause slight lenticular opacities in rats when administered orally for 2 months at a dose of 400 mg/(kg·d). Pefloxacin induces irreversible lenticular opacities in a dose-related manner in dogs given up to 200 mg/(kg·d) orally for 8 months [6, 18]. The relevance of these findings to long-term therapy in humans remains unclear. An important question is whether the lens and the aqueous humor of the eye act as deep compartments for some quinolones; pharmacokinetic investigations comparing quinolone concentrations in plasma with those in the lens capsule/nucleus and in the aqueous humor may provide the answer to this question. In addition, studies with animals on the cataractogenic potential of quinolones in association with other drugs are needed.

Effects on Spermatogenesis

Impaired spermatogenesis and/or testicular damage (atrophy in rats and dogs) have been described in long-term toxicity studies with some of the quinolones (e.g., pipemidic acid, norfloxacin, and pefloxacin); in these investigations the drugs were administered orally for longer than 3 months at doses of 100 mg/(kg·d) [16, 18]. Neuroendocrine mechanisms (the pituitary gland and gonadotropin release?) may be involved in these effects. Testicular damage has also been described in experiments with antibacterial drugs of other chemical classes, including aminoglycosides and cephalosporins.

Drug Interactions

Data on the possible influence of quinolones on hepatic drug-metabolizing systems are scarce. Nalidixic acid at high doses (≥200 mg/kg) prolongs hexobarbital-induced sleeping time in mice [18]. In humans, theophylline clearance is decreased by enoxacin (400 or 600 mg twice daily) [19–21], ciprofloxacin (500 or 750 mg twice daily) [20, 22, 23], pefloxacin (400 mg twice daily) [20], and ofloxacin (400 mg twice daily) [24]. Under steady-state conditions, enoxacin (400 mg twice daily) decreases antipyrine clearance [25]. The results of preliminary studies suggest that enoxacin (400 mg twice daily) also decreases the clearance of caffeine when the two drugs are given concomitantly [26].

These limited data require further investigation. It may be that quinolones of the naphthyridine type (e.g., nalidixic acid and enoxacin) may interact with purine compounds because of similarities in chemical structure.

The findings mentioned can be interpreted as representing an inhibition of drug-metabolizing enzymes. It is doubtful, however, that quinolones such as enoxacin are "classic" inhibitors of the microsomal drug-metabolizing systems, such as metyrapone and SKF 525 A (β-diethylaminoethyldiphenyl-propyla-

cetate hydrochloride). In our own experiments in rats on the *N*-demethylation of theophylline and of central-acting analgesics (tilidine and tramadol), we detected no inhibitory effect of prior enoxacin administration (40 mg/kg orally, 2 hours before the analgesics) (W. Christ et al., unpublished observations).

When combined with fenbufen (a nonsteroidal antiinflammatory drug), enoxacin may in rare instances cause convulsions in humans. When we administered a single dose of fenbufen (100–400 mg/kg) 10 minutes before enoxacin, ciprofloxacin, pefloxacin, norfloxacin, or fleroxacin (100–1,200 mg/kg), we observed tonic convulsions in mice and rats in all cases but one (ofloxacin) (W. Christ et al., unpublished observations). Schlüter and Mayer have reported similar results (personal communication). The biochemical mechanism of this interaction is unknown.

Cardiovascular Effects

After rapid intravenous administration of 10–30 mg/kg to anesthetized cats and dogs, most of the quinolones produce systolic and diastolic hypotension. It has been proposed that these cardiovascular effects are not caused directly by the quinolones but are mediated by histamine release. The intensity and duration of the effects are dose related. Thus, quinolones intended for intravenous use should be administered as an infusion. Hypotension and tachycardia have also been seen after oral administration of quinolones.

Mutagenicity

The question of whether quinolones are mutagenic and/or carcinogenic cannot be answered definitely because long-term carcinogenicity studies in animals have been completed only for norfloxacin. In rats, norfloxacin has no carcinogenic or toxic potential. At the doses tested—up to 600 mg/(kg·d) orally—no ocular abnormalities attributable to treatment were observed.

With some of the quinolones, the unscheduled DNA synthesis test on rat hepatocytes and the mouse lymphoma test gave positive results. Recent reports indicate that false-positive results may be obtained in these tests with quinolones, probably as a result of changes in the ionic strength of the test medium and incorrect evaluation of the test. Quinolones inhibit the replication of mitochondrial DNA in mammalian cells in a dose-related manner [27]. This effect must be taken into consideration when unscheduled DNA synthesis is quantified by counting of the grains. In most publications only the net nuclear grain counts are given.

To our knowledge, the quinolones are nonmutagenic. They inhibit bacterial gyrase. Primate cells also possess a gyrase (topoisomerase II), but this enzyme has an affinity for the quinolones that is several thousand times lower than that of bacterial gyrase. The detection of possible interactions between the quinolones and the primate genome is important, especially in the development of new quinolones with chemical characteristics and antibacterial potencies different from those of quinolones of the norfloxacin generation.

Photosensitivity

Various quinolones have produced photosensitivity in humans. Pefloxacin, nalidixic acid [6, 28, 29], and (to a lesser extent) other derivatives may cause mild to severe reactions when the skin of treated individuals is exposed to sunlight. With tetracyclines, phototoxicity is evident only when the skin is exposed to light containing rays with wavelengths in the range of 270–320 nm [29], which are filtered out by ordinary window glass. This observation may also apply to the quinolones.

Adverse Reactions to Quinolones in Humans

The pattern of adverse reactions is comparable for all quinolones, although there are slight differences in both the incidence and the type of reactions induced by certain compounds. The major categories of adverse reaction are gastrointestinal, dermatologic, hypersensitivity, cardiovascular, CNS and peripheral nervous system, special senses (diplopia, abnormal color vision, eye pain, tinnitus, impairment of taste and/or smell), hematologic, hepatic (elevation of hepatic enzyme levels and serum bilirubin concentrations), renal (elevation of serum creatinine levels, crystalluria, cylindruria, and hematuria), and musculoskeletal (arthralgia and myalgia).

The CNS effects of quinolones can be moderate, including headache, dizziness, light-headedness, and sleep disorders (both insomnia and somnolence). Further information is needed on severe CNS reactions, such as confusion, hallucination, anxiety, agitation, nightmares, convulsive seizures, depression,

and manic reactions. Unlike many antibacterial drugs, the quinolones can cause these severe CNS effects even after short-term use and administration of standard doses in patients with no abnormal psychiatric history. Only sulfonamides, nitroimidazoles (metronidazole), chloroquine, and some drugs used in chemotherapy for tuberculosis (e.g., isoniazid and cycloserine) have a comparable pattern of CNS effects [30, 31]. The available data on the incidences of adverse reactions to the newer quinolones (e.g., norfloxacin, ofloxacin, ciprofloxacin, and enoxacin) have different origins and therefore vary somewhat in validity. For ciprofloxacin and enoxacin, the incidence of adverse reactions have come mainly from clinical trials involving 9,000 and 5,000 patients, respectively. For norfloxacin and ofloxacin, these figures have come primarily from postmarketing studies and from spontaneous reports monitored by a mandatory reporting system; the basis for the reported adverse reactions are ~1.7 million prescriptions for norfloxacin and ~2 million prescriptions for ofloxacin (as of the end of 1986) in Germany. With norfloxacin, more than 8 million patients have been treated worldwide.

The overall incidence for all adverse reactions reported ranges from 4.4% to 16.5%. The most frequently reported effects are gastrointestinal (nausea, diarrhea, vomiting), with an incidence of 0.8%–6.8% [2]. The incidence of hypersensitivity and skin reactions is 0.4%–2.1%. That of CNS and peripheral nervous system reactions is 0.9%–2.1%; severe CNS reactions such as hallucinations, depression, nightmares, confusion, and manic reactions apparently occur in <0.5% of cases. Convulsive seizures are rare events: two of 8,861 patients treated with ciprofloxacin and three of 28,597 patients treated with norfloxacin have had convulsions. Epileptic seizures and similar reactions have been observed in nine patients given ofloxacin (described in spontaneous reports). In many cases these patients had a history of epilepsy or cerebral trauma.

Severe CNS reactions to norfloxacin (anxiety, agitation, depression, confusion) seemed to be quite rare [1, 4]. Moreover, this quinolone has been marketed only for the treatment of urinary tract infections in Germany, and the underlying infection (with the accompanying high fever) may explain some CNS symptoms [32].

All other adverse reactions—such as photosensitivity; cardiovascular effects; hematologic effects; and effects on renal and hepatic function, on special senses (diplopia, abnormal color vision, eye pain, tinnitus, impairment of taste and/or smell), and on the musculoskeletal system—have been reported at an overall incidence of 0.5%–2%. Of all of the newer quinolones, pefloxacin is most likely to be associated with photosensitivity.

Drug Interactions of Clinical Importance

Antacids containing magnesium hydroxide or aluminum hydroxide may interfere with the absorption of most of the quinolones, resulting in markedly decreased serum and urine levels; concurrent administration of these agents with quinolones should be avoided. In addition, the concurrent use of some of the newer quinolones (e.g., enoxacin, ciprofloxacin, and pefloxacin) with theophylline may lead to elevated plasma concentrations of theophylline and prolongation of the elimination half-life of the latter drug. These effects may in turn result in an increased risk of theophylline-related adverse reactions. If concomitant use cannot be avoided, plasma levels of theophylline should be monitored and dosage adjustments made. As has been mentioned, enoxacin also decreases the clearance of caffeine. Moreover, when combined with fenbufen, enoxacin may cause convulsions in humans; the concomitant administration of these two agents should therefore be avoided.

Precautions and Contraindications

A history of hypersensitivity to a quinolone indicates that no quinolone should be used. Because quinolones may cause CNS stimulation leading to tremor, restlessness, confusion, or (rarely) hallucinations or convulsive seizures, this class of drugs must be used with caution in patients with known or suspected CNS disorders (e.g., severe cerebral arteriosclerosis or epilepsy). Furthermore, since quinolones cause arthropathy in immature animals, these agents must not be used in pregnant or lactating women or in children or adolescents whose growth is not yet complete.

Conclusion

Quinolones are clearly a safe and effective addition to the armamentarium of antibacterial drugs. Initially, their greatest use will be in urinary tract infections, gonorrhea, and diarrheal diseases. How-

ever, they also can be used for the treatment of infections of the respiratory tract, skin structures, and (in particular) bone.

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