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Review

Quinolone-induced arthropathy: an update focusing on new mechanistic and clinical data

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ABSTRACT

Quinolones possess favourable antibacterial and pharmacokinetic characteristics and are often used as anti-infective agents in adults. They are contraindicated in children and adolescents because they damage weight-bearing joints in juvenile animals. In addition, they possess a tendotoxic potential. Since ciprofloxacin has been used off-label for decades in children and adolescents, it is known today that no pronounced risks for arthropathies or tendinopathies exist in humans. Recently published clinical studies with gatifloxacin in children support this clinical experience. However, a low risk for joint disorders cannot be excluded and tendinopathies are a generally accepted rare adverse effect of quinolones at least in adults. Isolated case reports of arthralgia in children following quinolone therapy have been published and in studies with levofloxacin the incidence of musculoskeletal disorders was significantly greater in levofloxacin-treated patients than in control patients treated with comparator antibiotics. As a consequence, only life-threatening infections for which other antimicrobials cannot be used are possible indications for quinolones in children, for example the use of ciprofloxacin in cystic fibrosis patients with a bronchopulmonary exacerbation, chronic suppurative otitis media caused by *Pseudomonas* sp., complicated urinary tract infections and enteritis caused by invasive multidrug-resistant pathogens (e.g. *Salmonella*, *Shigella*).

1. Introduction

Quinolones are contraindicated during pregnancy and lactation as well as in children and adolescents. Only a few exceptions to this rule are accepted. This restrictive use of a valuable class of antimicrobial agents is mainly based on toxicological findings in animals during postnatal growth. The results derive from studies that were conducted in addition to the routinely performed toxicological tests. The strict attention to these toxicological findings was often criticised. Some authors regard the quinolone-induced arthropathies as irrelevant for humans and demand a broad use in paediatric indications. The discussion about using quinolones in paediatrics has been intensified by the development of quinolones that are effective against penicillin-resistant pneumococci, for example gatifloxacin, levofloxacin and moxifloxacin. During recent years the benefits and risks of new quinolones have been studied in several paediatric clinical trials. The relevant experimental and clinical data published so far will be reviewed here, with a focus on the recently published clinical studies.

2. Chondrotoxicity of quinolones in animal testing

Initial papers describing quinolone-induced chondrotoxicity in growing animals were published ca. 30 years ago. In juvenile dogs treated with pipemidic acid, toxic effects on the immature joint cartilage were described for the first time in 1977 [1]. The authors observed stiffness of gait in these animals and found that the younger the animal, the earlier the onset of signs of arthropathy. These findings were confirmed a few years later in other studies. Blister formation and lesions in the immature articular–epiphyseal cartilage complex were demonstrated in quinolone-treated dogs at autopsy. Microscopically, a loss of proteoglycans and degenerated or necrotic chondrocytes as well as a disintegrated extracellular matrix were shown to be typical features of this toxic effect. Gait abnormalities in these animals were reversible, but lesions were detectable histologically in all dogs even several months after treatment (for review see [2,3]).

Chondrotoxicity in dogs is induced by some quinolones at doses as low as 10 mg/kg body weight. In other animal species, such as rats, higher doses are necessary to induce joint defects. However, despite these high doses, chondrotoxic concentrations of the drugs in plasma correspond to plasma levels achieved during therapy in humans. For correct interpretation of the findings in rat stud-

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ies, plasma levels are more meaningful than the doses because major differences of quinolone pharmacokinetics exist between the species [4].

In addition to the effects on immature joint cartilage in animal experiments, changes in the epiphyseal growth plate have also been described, which are associated with reduced growth of the humerus and femur of rats [5,6].

In recent years, quinolones have become more relevant due to the new derivatives gatifloxacin, levofloxacin and moxifloxacin exhibiting enhanced activity against pneumococci. The first two of these quinolones have been tested in paediatric clinical trials and therefore toxicological data are briefly described here. The results of these pre-clinical studies were not published, but details of the findings are available from the 'Full Prescribing Information' for Tequin™ and Levaquin™.

Arthropathy and chondrodysplasia were observed in immature dogs given 10 mg/kg gatifloxacin orally for 7 days (approximately equal to the maximum human dose based on systemic exposure). In an additional study in immature dogs given gatifloxacin orally for 2 weeks with a 6-month recovery period, articular cartilage lesions were observed at ≥5 mg/kg (ca. 30% of the human therapeutic dose levels based on plasma area under the concentration–time curve (AUC) comparisons), and growth plate cartilage lesions were seen at 10 mg/kg and 20 mg/kg. Articular cartilage changes seen on gross pathology and histopathology persisted through the 6-month recovery period, whereas growth plate cartilage lesions were resolved [7].

Similar results were obtained with levofloxacin. Three-month-old beagle dogs dosed orally with levofloxacin at 40 mg/kg/day exhibited clinically severe arthrotoxicity. Slight musculoskeletal clinical effects, in the absence of gross pathological or histopathological effects, resulted from the lowest dose level of 2.5 mg/kg/day (ca. 20% of the paediatric dose based upon AUC comparisons). Synovitis and articular cartilage lesions were observed at the 10 mg/kg and 40 mg/kg dose levels. Articular cartilage gross pathology and histopathology persisted to the end of the 18-week recovery period for those dogs from the 10 mg/kg/day and 40 mg/kg/day dose levels [8].

3. Tendinopathies

Besides their effects on immature joint cartilage and growth plates, quinolones can also affect tendons [3,9]. An inflammatory reaction with an oedematous swelling of the tendon is often described as an initial event. Symptoms can continue up to several weeks and may result in complete tendon rupture [10]. Even after an asymptomatic latency period of some weeks, a rupture of the tendon may occur. Often the Achilles tendon is affected. Tendinopathies have been described in association with all quinolones used today for anti-infective therapy. Data allowing substantial determination of the incidence of tendon disorders during quinolone therapy are not available. In a retrospective study, four cases of tendinitis were identified among 400 patients treated with ofloxacin. Nearly all cases of tendinopathies described so far occurred in adult patients. A possible risk factor for this adverse effect appears to be age >60 years, but inflammation and tendon rupture have also been described for younger patients. In 42 case reports published by a group of scientists from The Netherlands, ca. 20% of the patients were younger than 50 years of age [9,11]. So far, an estimation of the possible risk for tendinopathies in children has not been possible because these drugs are used almost exclusively in adults and tendinopathy is a rare side effect. Interestingly, juvenile rats were more sensitive for tendon alterations than adult rats [12]. It is assumed that the pathomechanisms of quinolone-induced arthropathy and tendinopathy are closely related, although the experimental and clinical data appear to indicate that arthropathy is a problem of the immature and tendinopathy is a problem of the aged organism [3,13,14].

4. Possible mechanism responsible for chondrotoxic and tendotoxic effects

A possible mechanism for the quinolone-induced arthropathy and tendinopathy, postulated on the basis of published biochemical and ultrastructural findings, involves impaired function of β_1 integrins as an initial event resulting in disturbed signal transduction between the extracellular matrix and chondrocytes (Fig. 1).

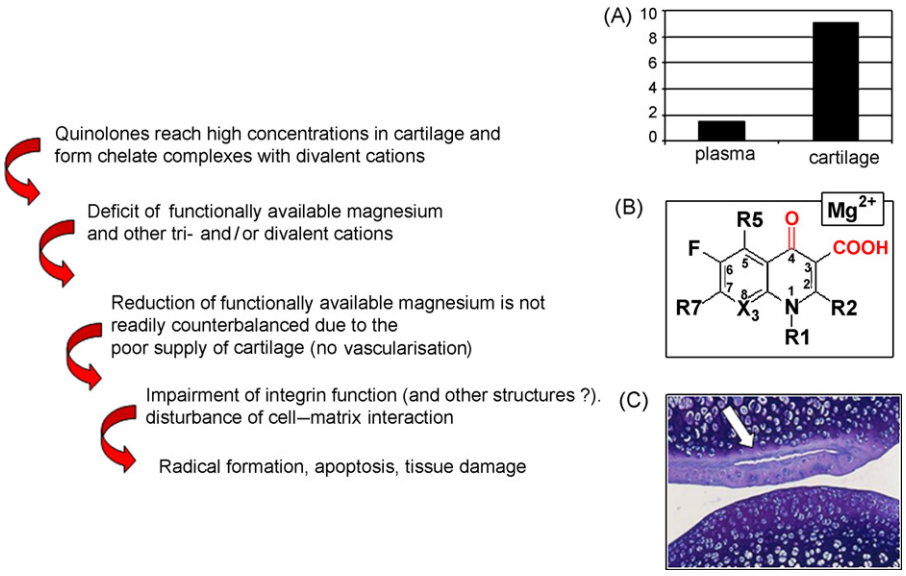

Fig. 1. Hypothetical pathomechanism of quinolone-induced chondrotoxicity. Sequence of events leading from chelation of magnesium to damage of the immature articular–epiphyseal cartilage complex. (A) Quinolones reach significantly higher concentrations in cartilage than in plasma. Concentrations were measured in plasma and cartilage from juvenile rats 6 h after single treatment with 100 mg ofloxacin/kg body weight orally (unpublished data from our laboratory). (B) All quinolones form chelate complexes with magnesium. (C) Knee joint of a juvenile rat after treatment with a quinolone (arrow indicates a typical lesion in the femoral part of the knee joint; the tibial part is unaffected).

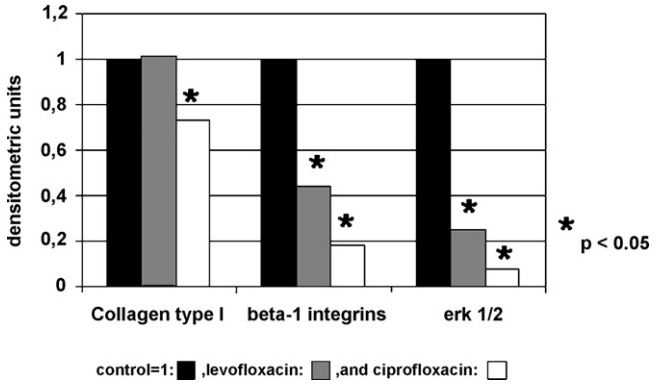

Fig. 2. Effects of ciprofloxacin and levofloxacin on proteins of the extracellular matrix or proteins involved in cell–matrix interactions and signalling in human tenocytes in vitro. Results of a Western blot analysis after 4 days of incubation with 10 mg/L ciprofloxacin or levofloxacin in comparison with an untreated control. Specific antibodies against collagen type I, β_1 integrins and extracellular signal regulated kinase (erk) 1/2 were used. Mean values of three Western blots are presented; asterisks indicate a significant difference in comparison with the controls (ANOVA followed by a post hoc Dunnett-*t*-test) (modified after [14]).

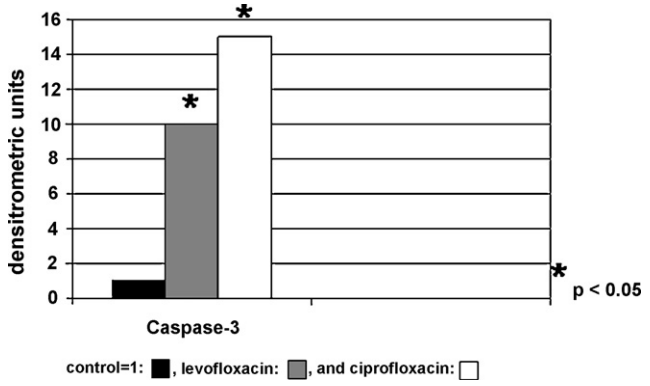

Fig. 3. Effects of ciprofloxacin and levofloxacin on caspase-3 in human tenocytes in vitro. Results of a Western blot analysis after 4 days of incubation with 10 mg/L ciprofloxacin or levofloxacin in comparison with an untreated control. A specific antibody against activated caspase-3 was used. Mean values of three Western blots are presented; asterisks indicate a significant difference in comparison with the controls (ANOVA followed by a post hoc Dunnett-*t*-test) (modified after [14]).

Owing to their chelating properties, quinolones form complexes with magnesium ions and thus interrupt the normal function of the signal receptors of the β_1 integrin family, the regulation of which crucially depends on magnesium. Consequently, essential cell–cell and cell–matrix interactions are disturbed resulting in radical formation and destruction of the tissue [14–16]. Additionally, β_1 integrins activate the mitogen-activated protein kinase (MAPK) signal transduction pathway. In vitro data show that this pathway is important for differentiation and survival of chondrocytes. Inhibition of the MAPK signal transduction pathway in chondrocytes resulted in apoptotic cell death [17]. In microencapsulated chondrocytes from juvenile rabbits, ofloxacin markedly causes apoptosis via the caspase-8-dependent mitochondrial pathway by affecting the levels of β_1 integrins and extracellular signal-regulated kinase (ERK)/MAPK signalling pathway. Using specific caspase inhibitors it was demonstrated that ofloxacin increased the level of Bax, tBid and p53 in a concentration- and time-dependent manner [18,19].

As a consequence of the disturbed interaction between matrix and cells, pronounced degradation of the extracellular matrix is observed. Fig. 2 shows the decrease in main matrix protein collagen type I, the transmembrane β_1 integrins and the erk 1/2 protein in human-derived tenocytes incubated with 10 mg/L ciprofloxacin or levofloxacin. For all proteins studied, the effects were more pronounced with ciprofloxacin than with levofloxacin. For the in vivo situation, the differences in pharmacokinetics between these drugs must be considered. Obviously these changes result in a pronounced increase of apoptosis. Fig. 3 indicates an up to 15-fold increase of caspase-3 protein in tenocytes following exposure to ciprofloxacin or levofloxacin.

Divalent cations such as magnesium are essential for a countless number of reactions in the mammalian organism. Specificity of the observed toxic effects on connective tissues might be explained first by an accumulation of quinolones in cartilage or tendon. In addition, and even more importantly, it has to be considered that connective tissues are bradytrophic, i.e. there is no direct blood supply in joint cartilage. A deficiency of electrolytes is therefore compensated more slowly than in other tissues (Fig. 1). In a series of experiments with juvenile rats, we have shown that a dietary magnesium deficiency induces changes in cartilage that are identical to those of quinolone-induced arthropathy. A combination of moderate magnesium deficiency and low doses of a quinolone turned out to be chondrotoxic, although both treatments by themselves caused no effects. Otherwise, additional administration of magnesium or tocopherol reduces quinolone-induced disorders, indicating that magnesium deficiency as well as radical formation plays a crucial role in the pathogenesis of quinolone-induced disorders of connective tissues [3,4,20–23].

5. Clinical experience with quinolones in children

Until now, chondrotoxic effects of quinolones on immature joint cartilage have been proven only in animal testing, and case reports are always associated with considerable uncertainty with respect to a causal relationship (e.g. [24]). Pefloxacin was used in France for children with cystic fibrosis (CF) and *Pseudomonas* infections before ciprofloxacin became available. It possibly caused some quinolone-associated arthropathies described by French authors as early as 1989 [25]. Most experience with quinolone use in juvenile patients is available for ciprofloxacin. This quinolone has been used in children predominantly with CF and bronchopulmonary *Pseudomonas* infections on a compassionate-use basis. The rate of joint disorders in children under these conditions was low and symptoms must be regarded primarily as a complication of the underlying CF disease [26,27].

Recognising the difficulties in discriminating between quinolone-induced joint complaints and similar symptoms with other causes, it is necessary to study not only quinolone-treated children but a control group as well. In a retrospective analysis of data from health insurances between 1992 and 1998, more than 6000 children and adolescents treated with a quinolone were compared with 15 000 children and adolescents treated with azithromycin. Most patients were older than 10 years, and ca. 500 children between 2 years and 9 years received ciprofloxacin. Regarding joint or tendon disorders, no significant difference was seen between the azithromycin- and ciprofloxacin-treated children. The incidence in the quinolone group was 0.82% compared with 0.78% in the azithromycin group [28].

Besides clinical experience, some retrospective studies and case reports, a risk–benefit analysis today can also be based on several prospective clinical studies with quinolones in paediatric patients. In a direct comparison between trovafloxacin and ceftriaxone of ca. 100 children with bacterial meningitis, one case of joint disorder was observed in the trovafloxacin group and three cases in the comparator group [29]. In Bangladesh, a comparative trial between a single dose of ciprofloxacin (20 mg/kg) and 3-day erythromycin therapy in children from 2–15 years with cholera was performed.

Table 1
Adverse events due to gatifloxacin and amoxicillin/clavulanic acid in patients with recurrent acute otitis media and/or acute otitis media treatment failure in phase II and III studies (modified after [32])

	Gatifloxacin (phase II)	Gatifloxacin (phase III)	Amoxicillin/clavulanic acid (phase III)
Patients			
N	414	453	309
Aged <2 years (*n*)	N.S.	188	137
Adverse events (*n* (%) of subjects)			
Drug-related	86 (20.8)	91 (20.1)	66 (21.4)
Resulted in discontinuation of study regimen	31 (7.5)[a]	7 (1.5)	7 (2.3)
Drug-related (severe)	1 (0.2)	0	1 (0.3)
Arthropathy	5 (1.2)[b]	7 (1.5)	4 (1.3)
Tendinitis	A 4-year-old child, 5 days after completing treatment with gatifloxacin[c]		

N.S., not specified.
[a] The high rate of discontinuation is caused by emesis due to the bitter taste of the drug formulation. In phase III studies an optimised formulation was used.
[b] Two of 254 treated children in a phase II study [33] discontinued therapy owing to joint pain.
[c] Not specified if phase II or phase III trial.

Ciprofloxacin was more effective and better tolerated. No joint disorders were observed [30]. Ciprofloxacin was compared with a cephalosporin for the treatment of complicated urinary infections or pyelonephritis in a total of 684 paediatric patients aged 1–17 years (mean 6 ± 4 years). The rates of events such as arthralgia, bone pain, myalgia, arm or leg pain etc., within 6 weeks of treatment initiation were 9.3% (31/335) in the ciprofloxacin-treated group versus 6.0% (21/349) in comparator-treated patients (95% confidence interval (CI) −0.8% to +7.2%) [31]. Most extensive clinical studies have been performed with gatifloxacin and levofloxacin. Data from four paediatric phase II and III studies are available for gatifloxacin. In total, 867 children between 6 months and 7 years with recurring otitis media or failure of the primary therapy against otitis media were studied.

Gatifloxacin showed a significantly higher cure rate than the comparator amoxicillin/clavulanic acid. A reasonable explanation for the improved efficacy is the activity of gatifloxacin against penicillin-resistant pneumococci. The results of all studies as well as a safety analysis of the pooled data were published by an international group of paediatricians. Some of these results are compiled in Table 1 [32].

A transient arthralgia was observed in 12 (1.4%) of 867 gatifloxacin-treated children (phase II and phase III studies). Disorders resolved within 2 weeks without requiring treatment. Seven of these twelve children were examined by an orthopaedist or paediatric rheumatologist, but no abnormal findings were detected. Magnetic resonance imaging (MRI) examination of two children showed no evidence of arthrotoxicity. One child discontinued therapy because of a transient left knee arthralgia associated with joint swelling and abnormal gait. MRI examination revealed no joint abnormalities, and multiple subsequent joint examinations during a 12-month follow-up period revealed no joint abnormalities in this child. Phase III studies demonstrate a similar incidence of arthralgia in the gatifloxacin group (1.5%) and in children treated with amoxicillin/clavulanic acid (1.3%). One-year safety follow-up data were collected for 671 gatifloxacin-treated children. In this second examination of 671 children, no evidence of arthropathy was reported. The study had 80% power to detect events occurring at a rate of $\geq$0.25%. Moreover, children treated with gatifloxacin grew at normal rates, according to standardised growth rates. Within 12 months, no difference was detected between the gatifloxacin and amoxicillin/clavulanic acid groups.

A 4-year-old girl developed pain of the Achilles tendon 5 days after completing treatment with gatifloxacin. The investigator judged the severity of the pain as 'moderate' and 'possibly related to the study drug'. Disorders were treated by cooling and rest and were reversible within 5 days [32]. Corresponding case reports regarding possibly quinolone-related reactions of the Achilles tendon in children at the age of 4 years have not been published so far. The described clinical studies were sponsored by the pharmaceutical company producing the gatifloxacin drug Tequin™. Bristol-Myers Squibb was willing to have a restricted label for the treatment indication (i.e. recurrent otitis media or after failure of other antibiotics). As part of their risk management plan, the company had agreed to initiate a prospective post-marketing study that would observe 4000 children for 5 years to prove statistically that the risk of arthrotoxicity was <0.1%. However, Bristol-Myers Squibb finally withdrew the new drug application because of the inability to construct a plan agreeable to the US Food and Drug Administration (FDA) and Bristol-Myers Squibb that could limit the use to the appropriate patients, i.e. those with recurrent acute otitis media or for whom other therapy had recently failed [34].

Another quinolone that was tested in several large clinical trials in children older than 6 months is levofloxacin. In one study, which was conducted at 43 centres in seven countries, paediatric patients with community-acquired pneumonia were treated orally and/or intravenously. A diagnosis of pneumonia was defined as clinical plus radiological evidence of pulmonary infiltrate consistent with acute infection requiring antibiotic therapy; only 36% of the children were diagnosed with a specific aetiology at admission to the trial. In the open trial the following antibiotics were used as comparators: amoxicillin plus clavulanic acid or ceftriaxone in children between 0.5 years and 5 years; and a macrolide (e.g. clarithromycin), possibly in combination with ceftriaxone, in children between 5 years and 16 years old. *Mycoplasma pneumoniae* was the most frequently identified cause of pneumonia. Clinical cure rates after 10 days of treatment were ca. 94% in both groups, and cure rates were similar for both age groups. Levofloxacin was as well tolerated as comparators; gastrointestinal symptoms such as nausea, vomiting or abdominal pain were most common [35].

In another open clinical trial, levofloxacin was used in children at an age from 6 months to 5 years with recurrent or persistent otitis media. The drug was given at a dose of 10 mg/kg twice daily (b.i.d.) for 10 days. Persistent acute otitis media was defined as evidence of otitis media on the third day after starting any antimicrobial treatment. A sample of middle ear fluid for microbiological diagnosis was obtained by tympanocentesis. The clinical success rate after therapy was 94% for the total study population and 92% for the bacteriologically evaluable population [36].

An analysis of the safety data from these two trials and one further clinical trial of levofloxacin in children was performed to identify possible specific musculoskeletal disorders. The analysis focused on four musculoskeletal disorders considered to be biologically relevant to the findings in animals: arthritis; arthral-

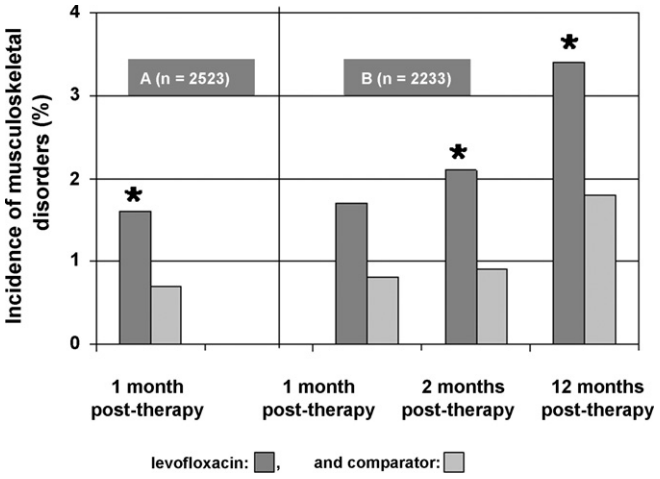

Fig. 4. Incidence of musculoskeletal disorders (arthralgia, arthritis, tendinopathy and gait abnormality) in phase III trials with levofloxacin in comparison with other antibiotics and long-term surveillance trial. Asterisks indicate a significant difference in pair-wise comparison of levofloxacin and comparator arms using two-sided Fisher's exact test (modified after [37]).

gia; gait abnormality; and tendinopathy. A total of 2523 children had been treated in the phase III studies (levofloxacin, $n = 1534$; comparator, $n = 989$) and almost 90% of these children ($n = 2233$) also subsequently participated in a long-term 1-year surveillance trial. A similar incidence and character of adverse events was observed with levofloxacin during and for 1 month after therapy; musculoskeletal events were noted in 3% of the patients in both groups. However, when the incidences of the predefined set of musculoskeletal disorders (arthritis, arthralgia, gait abnormality and tendinopathy) were assessed, differences between levofloxacin- and comparator-treated children were evident (Fig. 4): 1.6% of the levofloxacin-treated children had musculoskeletal disorders (25/1534) compared with only 0.7% (7/989) in the comparator group ($P = 0.046$). In the subset of these patients who completed the long-term surveillance trial the difference between the groups at 1 month post therapy was not significant ($P = 0.063$), but incidence of at least one of the four predefined disorders (largely due to reports of arthralgia) was greater in levofloxacin-treated patients at 2 months (2.1% vs. 0.9%; $P = 0.04$) and 12 months (3.4% vs. 1.8%; $P = 0.03$) after starting therapy. The median duration of these disorders was 7 days and 9 days in the levofloxacin group and the comparator group, respectively [36].

A detailed description of the character of the musculoskeletal disorders that occurred in the 46 levofloxacin-treated children (3.4%) and the 16 comparator-treated children (1.8%) during the 12-month observation period is presented in the publication [37]. Five levofloxacin-treated children with musculoskeletal disorders underwent MRI or computed tomography (CT) examination. No abnormalities were found in these assessments. One child treated with levofloxacin was identified by the 'Data Safety Monitoring Committee' as having impaired growth. On Day 173 of his long-term evaluation, when he was 18 months of age, this boy was reported to be delayed in walking. This resolved 33 days later when he began to walk. At his final evaluation before being lost to follow-up, although the child's height was above the 50th percentile for his age, he had achieved <80% of his expected growth over the 1-year period following treatment with levofloxacin (G.J. Noel, personal communication). One girl of 11.6 years developed two periods of tendonitis with onset on Days 11 and 173. Among the 16 comparator-treated children, one girl aged 7.4 years suffered from a tendinopathy as a result of a traumatic injury.

The authors discuss that if a broader definition for the adverse events had been used, differences between levofloxacin-treated and comparator-treated children would not have been evident. However, it has to be considered that parents were informed as part of their child's participation in the non-blinded trials about the potential of fluoroquinolones to be associated with joint disease, and the potential for biased reporting is clear. Consequently, the interpretation of the observed musculoskeletal disorders as a proven, definitely drug-induced adverse effect has been criticised [38]. Nevertheless, it is generally accepted that quinolones should not be used in paediatrics for routine treatment if safe and effective alternatives are available.

Not only for toxicological reasons, but also because of the threat of an increase in bacterial resistance, it is appropriate to restrict the use of quinolones in paediatrics. Owing to the experience with other groups of antibiotics, a more rapid selection of resistant pneumococci in children compared with adults seems to be likely. A horizontal transfer of quinolone resistance from viridans group streptococci (*Streptococcus mitis*, *Streptococcus oralis*), which belong to the normal human flora, to *Streptococcus pneumoniae* is possible. Quinolone-induced resistance in the natural commensal bacteria carries the risk that the infecting strain of *S. pneumoniae* will readily acquire quinolone resistance-determining DNA regions when antimicrobial therapy is started. Eventually, a widespread dissemination of these resistant pathogens in the adult population is possible [39].

6. Differences in velocity of growth in animals and man: an explanation for the low risk of quinolone-associated toxicity in children?

The chondrotoxic risk associated with the use of quinolones in children is obviously low. Some authors even assume that the findings of animal testing are completely irrelevant for humans. However, a conclusive explanation for the fundamental difference in the reaction of connective tissues in man and in animals, which could explain the observed species differences, is not known. No major principal differences between the morphology or biochemical composition of the cartilage in animals and man are known. Since all animal species tested proved to be susceptible to the quinolone-induced toxic effects on cartilage and tendon, it is unlikely that these effects cannot occur in humans. For many compounds the differences between toxic effects observed in animals and man can be explained by the differences in dose levels or, more precisely, the differences in exposure based on the AUC. In the case of quinolone-induced chondrotoxicity, however, it cannot be ignored that the immature joint cartilage in juvenile dogs is damaged at dose levels (and exposure based on AUC values) that are below those that are used in children. Also in rats, which represent the species in which, besides dogs, most experiments were performed, cartilage changes occur at quinolone plasma concentrations that are achievable during therapy. Therefore, the high doses that have been used in some experiments to induce chondrotoxicity in juvenile rats are not a good argument to explain principal species differences.

One aspect that has not been discussed so far in this context is the velocity of growth, which shows major differences between the animals used in the toxicological evaluation and in children. The number, location and time of appearance of secondary centres of ossification varies between species [40]. Animals that are used in toxicological studies grow rapidly, but human growth extends over much longer periods, exhibits pronounced individual variability and cannot be viewed as a continuous process. Rather it is characterised by changing velocity with age. It has been shown

that growth in length occurs by discontinuous, aperiodic saltatory spurts. These bursts were separated by periods of 2–63 days duration with no measurable growth. In other words, 90–95% of normal development during infancy is growth-free [41]. Although these data have been criticised, it is undisputed that periods of no growth (stasis) are a common phenomenon in human growth [42–44]. If the assumption is correct that damage to the immature joint cartilage can only occur during growth periods, then the low degree of human susceptibility is explainable. It would explain why the quinolone-induced arthropathies are a rare adverse effect in children whilst immature animals develop symptoms in a more uniform way.

7. Selected indications for quinolone therapy in children

Over the past 10 years the Committee on Infectious Diseases of the American Academy of Paediatrics published several reviews and listed indications for which quinolones might be considered after careful individual consideration of the benefits and risks. These recommendations were supported by and commented upon several times by leading paediatricians [45–51]. Based on these statements, treatment with quinolones in paediatrics may be considered for the following diseases.

7.1. Exacerbations of pulmonary disease in patients with cystic fibrosis

Chronic bronchopulmonary infections are the most important complications of patients with CF. *Pseudomonas aeruginosa* can be found in the sputum of up to 90% of these patients. Ciprofloxacin given orally is as effective as treatment with a β-lactam plus an aminoglycoside. Oral administration of ciprofloxacin improves the child's quality of life because it allows an outpatient therapy. Extensive use of ciprofloxacin for this indication did not reveal an increased risk for definitely drug-induced joint disorders [27,49].

7.2. Complicated urinary tract infections

Urinary tract infections in patients with obstruction of the urinary tract are considered complicated infections. Over the past years, development of resistance in relevant pathogens against common anti-infective agents was noticed. For example, resistance to amoxicillin or trimethoprim/sulfamethoxazole (co-trimoxazole) increased rapidly. Most alternative agents can only be used parenterally. Therefore quinolones are often suggested as a possible alternative for children. Particularly if *P. aeruginosa* or other multidrug-resistant (MDR) pathogens are isolated, quinolones can be considered as a therapeutic option. However, published experience with quinolones in children is limited for this indication and the emergence of resistance among *Escherichia coli* in adults is of major concern.

In a multicentre study in children with complicated urinary infections or pyelonephritis and an average age of 6 years, the efficacy and tolerability of ciprofloxacin was tested and compared with a cephalosporin. The therapeutic efficacy was similar in both groups (ciprofloxacin 95.7% vs. comparator 92.6%). In the USA, ciprofloxacin is approved for therapy of complicated urinary infections or pyelonephritis of children aged 1–17 years. The recommended dose is 10–20 mg/kg orally (maximum 750 mg per dose) b.i.d. Although effective in clinical trials, ciprofloxacin is not a drug of first choice in the paediatric population owing to an increased incidence of adverse events compared with controls, including events related to joints and/or surrounding tissues [31].

7.3. Enteritis (e.g. transmitted by multiresistant Salmonella or Shigella spp.)

In developing countries, invasive gastrointestinal infections transmitted by MDR bacteria such as *Salmonella*, *Shigella*, *Vibrio cholerae* and *E. coli* often lead to severe and life-threatening infections. Because of their favourable pharmacodynamic and pharmacokinetic features, quinolones are qualified for therapy of severe diarrhoea caused by such pathogens. They possess high activity against Gram-negative bacteria and reach high concentrations in faeces as well as intracellularly, e.g. in phagocytes. A number of clinical studies are available that support their suitability. In children with cholera, a single dose of ciprofloxacin (20 mg/kg) was clinically successful in 60% of the patients compared with 55% of the children treated with erythromycin (12.5 mg/kg four times daily) for 3 days. However, in this study the single dose of ciprofloxacin was more often associated with bacteriological failure than the 12-dose macrolide therapy (58% vs. 30%) [30,46].

7.4. Chronic otitis media

A chronic suppurative otitis media is defined as a perforated tympanic membrane and discharge for at least 6 weeks. It is associated with a risk for severe intracranial complications. *Pseudomonas aeruginosa* can be detected in almost all of these cases. Under those rare circumstances, therapy with ciprofloxacin might be considered. Additionally, ciprofloxacin and ofloxacin can be used in ear drops for local therapy. Some authors also recommend quinolone use for complicated acute otitis media failing to respond to initial antibiotic treatment.

7.5. Prophylaxis of anthrax

A placebo-controlled study in rhesus monkeys exposed to an inhaled lethal dose of *Bacillus anthracis* spores was conducted. Mortality due to anthrax for animals that received a 30-day regimen of oral ciprofloxacin beginning 24 h post-exposure was significantly lower compared with the placebo group. Ciprofloxacin is recommended in the USA for the prophylaxis of anthrax for adults and children. It should be given within 24 h after an exposure and for 60 days overall with a dose of 15 mg/kg b.i.d.

7.6. Other possible indications

In addition to the above mentioned indications, quinolone therapy was proposed for life-threatening infections of the central nervous system or for cancer patients with neutropenia, in exceptional cases. However, all possible indications have in common, that they concern severe, potentially life-threatening diseases. Since the alternatives from the group of β-lactams can mostly be given by the parenteral route only, the possibility of oral therapy with quinolones bears a considerable advantage, particularly in children. The recommended use of quinolones in children and juveniles is very limited in view of the low risk of possible arthropathies or tendinopathies as well as concerns about the accelerated development of MDR pathogens.

8. Conclusions

In paediatrics, a very restrictive use of quinolones is still recommended, because: (i) a slight risk of quinolone-induced arthropathy cannot be excluded; and (ii) there are concerns about the rapid spread of resistant pneumococci. Treatment with a quinolone is only acceptable if, first, the patient suffers from a life-threatening or difficult-to-treat infection and, second, other antibiotics cannot

be used because the patient is allergic or does not tolerate the drug for other reasons, or the pathogen is resistant to other anti-infective drugs.

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