

Monofluoroquinolones (MFQs): Safety use in pediatrics (Clinical, Morphological and Follow-up Data)

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Abstract: 2 groups of children were included to assess monofluoroquinolones (MFQs) safety in open observational prospective study: 169 cystic fibrosis patients (pulmonary exacerbation phase) and 55 aplastic anemia patients (neutropenia phase) at age 6 months to 16 years treated with ciprofloxacin (CPF), ofloxacin (OF) or pefloxacin (PF) at different time points. Study purpose was to compare MFQS tolerability (arthropathy-focused mainly) in intermittent (treatment doses 15-50 mg/kg in cystic fibrosis patients) or uninterrupted prolonged use (prophylactic doses 10-15 mg/kg in aplastic anemia patients). It was showed (accumulated data in both groups) that quinolone arthropathy (QA) had developed in 8.4% of cases mostly in PF group (74%), more frequently in cystic fibrosis patients (CF) and exclusively in adolescents with full regression and without any height impact. Absence of residual arthrological symptoms and any height impact resulted from the fact that FQs are not cumulated in cartilaginous structures in chondrotoxic concentrations, and the occurrence of QA is caused by the development of synovitis as a result of individual FQs intolerance.

Keywords: Fluoroquinolones, Arthropathy, Linear Growth, Knee Joint Morphology

1. Introduction

First monofluoroquinolones (ciprofloxacin, ofloxacin, pefloxacin) were included as a therapy option in the mid-80 last century and soon got pediatricians' attention due to broad spectrum of an antimicrobial activity and a large volume distribution, a possibility to use the antibiotics (AB) at almost all infection locations, its ability to impact on microbes biofilm formation – one of the main resistance mechanism, and also a good tolerability in adults [1, 2].

Firstly fluoroquinolones (FQs) were used off label then FDA approved its use in children with cystic fibrosis (CF), anthrax and complicated pyelonephritis.

However legal noncompliance regarding these antimicrobial agents still exists: de facto widespread use in

pediatrics versus acting recommendations to avoid its use in children at least before pubertal age due to experimental disabling damage of weight-bearing joints in immature animals while using toxic doses of FQs (20-25 times exceeding therapeutic doses). Notably no FQs arthropathy was found in monkeys – an experimental model with a high degree of genetic relatedness to humans and in mice – a smallest experimental model with high drug clearance.

Looking through abundant FQs documentation surprisingly we did not find Russian data. That was a reason to fill the gap as in our 1000-bed children's hospital we have almost 30 years' experience of these AB use.

The aim of this investigation was to study of comparative safety of FQs (principally arthrototoxicity), to reveal risk factors of QA and basing on morphological and immunological studies to

express our point of view regarding QA pathogenesis.

2. Materials and Methods

Observational study (open, prospective) in 1993-2019 was developed in two phases.

2.1. Active Phase (1993 – 2006)

Two group of children who received ciprofloxacin (CPF), ofloxacin (OF), or pefloxacin (PF) at different times were assessed for FQs tolerability (arthropathy-focused) at that phase: CF patients (intermittent use in therapeutic doses) and aplastic anemia (AA) patients (uninterrupted use of prophylactic doses) (Table 1).

Table 1. General characteristics of CF and AA patients on FQs treatment.

Nosology	Cystic fibrosis			Aplastic anemia		
Drugs	CPF	OF	PF	CPF	OF	PF
Dose (mg/kg)	15-50	15-25	18-29	15	10	10
Number of patients	111	19	39	38	12	5
Age (years)	0,5 - 16	7-15	7-16	1.75 - 15	5-16	10-12
Gender F	52	10	26	21	8	9
Gender M	59	9	13	17	4	2
Total	169			55		

In CF group FQs were used for the period 15-21 days to treat an exacerbation of bronchopulmonary process, a total number of those courses during follow-up years varied from 2 to 35. FQs were always combined with other AB: 3rd generation cephalosporins, or aminoglycosides.

In AA group FQs were used as monotherapy for the whole duration of agranulocytosis (26-301 days) to prevent autoinfection (gut decontamination).

We tried to find a match to the experimental data while choosing the observational groups: wherein QA development were depending upon a dose and FQs use duration.

The University Ethic Committee has approved FQs use in all studied patients.

In active phase: besides visual assessment of developed QA and its triggers identification a postmortem knee-joint morphology was studied. Fluoride as FQs biomarker was quantified in osseous and cartilaginous tissue of knee-joint and the tablets of CPF, OF and PF at recommended dosage; in prolonged follow-up the developed arthropathy consequences were controlled and FQs impact on children height was assessed.

Phase II (2006-2019) - in phase II FQs tolerability was assessed by spontaneous reporting.

2.2. FQs Impact on Arthropathy Was a Main Concern in Light of the Study Purpose

Table 2. FQs tolerability (focus on arthropathy).

Nosology	Cystic fibrosis			Aplastic anemia		
Drugs	CPF	OF	PF	CPF	OF	PF
QA cases number	1	-	12	4	-	2
Age (years)	16	-	9-16	10-14	-	10-12
gender F	1	-	7	2	-	1
gender M	-	-	5	17	-	1
Total number of QA cases	13			6		

QA had developed similarly and specifically in all patients: a sudden onset on days 3-11 of CPF or PF use and only synovial type joint damages both weight-bearing – lower extremities (knee, ankle) and not weight-bearing – upper extremities (shoulder, elbow), showing its swelling without hyperemia or body temperature rise.

No case showed involvement of the spine - main human weight-bearing joint organ (122 joints). A spine has non-synovial type of binding in joints despite vertebrae are covered by the same hyaline cartilage as extremity joints. Also no damage to ligamentous apparatus of upper and lower limbs were found (above all, heel tendon).

The data presented in Table 2 made clear some features of identified QA: its drug-dependent character (none on OF therapy) and also its high frequency in CF patients. The last feature is easily explained as CF patients have a underlying predisposition to develop an arthropathy [3]: hypertrophic pulmonary osteoarthropathy and cystic fibrosis arthropathy.

It is not occasional that QA was developed in children at the age over 9 years: at the age 6-8 years' articular cavity and synovial membrane became mature as in adults' joints [4, 5] it means that QA in children (unlike the experiment) is an adult joint reaction.

Drug-dependent character of QA and its high frequency on PF therapy we explain by a few points.

Firstly we supposed that it can be related to the different fluorine content in CPF, OF and PF tablet. To support the assumption, we assessed F-ion content by ionometry (Analytical Chemistry Chair of MSU) – Table 3.

Table 3. Dosage strength, fluorides and fluorine in standard tablets and molecules of CF, OF and PF.

Drugs	CF	OF	PF
Tablet weight (mg)	250	200	400
Dosage strength in a tablet (mg)	26,9	12,4	57,4
Fluoride content in a tablet (mcg)	95	40	200
Fluorine content in a molecule (mcg)	5,0*10 ⁻⁶	2,1*10 ⁻⁶	10,5*10 ⁻⁶

In our opinion the table data clearly showed that QA, the direct fluorine-toxic effect of PF, more frequent than in other FQs, could be related to the bigger content of fluorine. Fluorine-dependent nature of arthropathy is also proven by the fact that QA development of PF treatment after OF or CF therapy switch has not reoccurred.

Moreover, PF has another important feature – strong immunomodulatory properties [6]: an ability to enhance IL-2 expression that further can be followed by T-lymphocytes activation and proliferation. Apparently, this mechanism has an important role in supporting QA genesis.

To confirm our suggestion on lymphocytic immunity (T-cell) role, we assessed plasma levels of the main anti-inflammatory cytokines IL-1 and TNF- α in four CF patients who experienced QA on PF treatment by ELISA method (Table 4).

Table 4. Anti-inflammatory cytokines plasma level in CF patients on PF treatment.

Patient (age)	PF dose (mg)	IL-1 N (0-50 mcg/ml)	TNF- α N (0-50 mcg/ml)
Patient K. I. (16 years)	800	1600	390
Patient K. N. (14 years)	800	12000	40
Patient L. Yu. (14 years)	800	40	360
Patient P. K. (10 years)	400	50	250

These particular cytokines are the main mediators of type IV hypersensitivity. One might recall that in our study QA had developed on Days 3-11 after FQs start. We think that namely cytokines toxic effects and not the FQs are responsible for the QA development. In this regard we have interesting data [7] that no PF was found in synovial fluid of knee-joint during QA peak associated with AB intake. Thus, it is possible that QA in children is developed not after FQs cartilage infiltration (as in the experiment), but passing through the synovial membrane with developed aseptic cytokine-induced inflammation, i.e. QA is a quinolone allergic synovitis.

For two patients we have cytokines levels follow-up (Table 5) showing a real concurrence between clinical and laboratory data. Accordingly the patient P. K. 10 years old had QA fully resolved in parallel with cytokines levels back to normal and other patient K. I. 16 years old, still had discomfort in knees when climbing down stairs and some functional limitations (difficulty jogging) in parallel with elevated cytokines levels.

Table 5. Cytokines plasma level in CF patients experienced QA 3 months after PF discontinuation.

Patient (age)	IL-1 N (0-50mcg/ml)	TNF- α N (0-50 mcg/ml)
Patient PK (10 years)	50	50
Patient KI (16 years)	1325	250

There is another mechanism of arthritis: cyclooxygenase-2 (COX-2) is an inflammatory enzyme produced by monocytes, synoviocytes and fibroblasts of the synovial membrane after different inducers action, including IL-1 and TNF- α . It is therefore NSAIDs use is necessary for QA targeting both COX-2 and cytokines.

Apart from cytokine-associated (T-cell-mediated) it is possible to have another immune mechanism in some cases. It is known [8], that arthralgia, one of serum sickness-like reaction (SSLR) findings, also at the background of CPF, has an immune complex syndrome – type III hypersensitivity.

So, QA may be caused by different mechanisms: fluorine-dependent or immune-mediated.

Nevertheless, the severity of the pathology can be determined only by prolonged follow-up and articular morphology regardless of the origin.

2.3. Arthrological Consequences and Linear Growth After FQs Use

During follow-up period of an active phase (1993 – 2006) two problems with the highest concern among the experts were studied: arthrological consequences after FQs use and

linear growth as in acute experiment in immature animals FQS induced disabling arthropathy (chondropathy) and growth stunting due to cartilage damage.

For this purpose, we chose two follow-up groups: 1st cohort – 205 CF patients and AA patients aged 0,5-16 years with no QA signs; 2nd cohort – 19 CF patients and AA patients aged 10-16 years who experienced QA. In the groups there was a joint examination 2-4 times a year, including external joint view, joint range of motions, physical activity rate.

In 1st group there were no any musculoskeletal disorders for 13 years of follow-up in spite of recurred or concomitant prolonged FQs use, i.e. there was no possible latent cartilage damage manifestation. Noteworthy, that it was not occurred in children who have been under FQs treatment since 6-month-old (3 children).

In 2nd group QA was reversible in all 19 patients with no residual symptoms response from 2 days up to 4 months. Regression had started right after “offending” drug discontinuation and accelerated after NSAIDs use, i.e. QA occurred and proceeded as acute reactive arthritis.

Required time for the QA recovery was dependent upon its initial symptoms. In this regard we consider it necessary to allocate two possible arthropathy forms under FQs use: arthralgic form – mild to severe pain only and arthritic form – pain, mild to moderate swelling, function limitation. Yet skin temperature measured in the axillary area (body temperature) and above joint was normal.

Arthralgic form of QA has resolved early and spontaneously after FQs discontinuation or after routine use of analgesics (paracetamol).

Arthritis (as any other reactive arthritis) has required NSAIDs administration (ibuprofen) until the relief of symptoms.

It should be noted, that arthralgic form of QA (of mild severity) was more common than arthritic form among our patients: 20.9% and 14.2%, respectively (accumulated data, both groups CF+AA).

In addition, 12 of 19 patients required a premature FQs withdrawal (the most frequently it was PF) due to severity of acute QA signs.

The evaluation of linear annual mean growth rate was carried out for 5 years in 58 CF patients aged 4-16 years: 38 children with prolonged CPF therapy and no QA signs (main group) and 20 children treated with other antimicrobial agents (control group).

Comparisons showed that CPF had no stunting impact on growth rate in children and notably in adolescence (9-16 years) – one of critical development periods in children: 5,4±0,6 cm in main group and 5,7±0,8 cm in control group ($p>0,05$).

So full QA reverse with no residual symptoms and equal in age linear growth in patients treated with FQs indirectly attests to the fact that these agents have no overt or latent chondrotoxic effect such as articular cartilage or growth plate damages.

However only focused morphological investigations

whether life-time (MRI) or postmortem can directly answer to a question about possible cartilage damage under FQs therapy.

MRI – an examination showing 3-dimensional picture of right knee joint at QA peak - was performed to exclude septic arthritis in AA patients but not aimed to scientific purpose. In this regard an equity and specific trend was captured: an accurate, even and undamaged cartilage and growth plate, thickened synovium. MRI-image of synovitis.

These data confirmed an assumption we have delivered earlier that QA develops not because of cartilage damage but due to FQs' passing through synovium.

3. Necropsy

For the postmortem exam of knee joint morphology a distal part of right femoral bone was extracted on an autopsy. The subject to investigate was cartilage, growth plate, cancellous bone, synovium status in 11 CF patients aged 3,5 – 16 years and 10 AA patients aged 1,75 – 16 years died of underlying disease progression, and none had any life-time QA signs. It was taken into account that cartilage damage in animals was not always gone along with the symptoms according to the experimental data and besides different FQs

dosing were considered in those patients (Table 6).

Table 6. Summary on knee-joint morphology in CF and AA patients.

Parameters	CF	AA
Patients number	11	10
Age (years)	3,5 - 16	1,75 – 16
CF dose (mg/kg/day)	15-50	15
Whole treatment period (days)	177 (30-340)	105 (12-190)
CF use	Intermittent	Continuous

Control group included 10 apparently healthy children at the age 6-14 years, died due to car accident.

Macroscopic view of cartilage, cancellous bone and growth plate were similar in two groups and aligned with the control one.

Histology examination (light microscopy) showed limited chondrocytes number increase in superficial layers of cartilage (hyperplastic reaction). In the growth plate was found ordinary structure of hyaline cartilage showing signs of interstitial expansion. In one case an inapparent synovitis was found.

The morphometric measures were in compliance with the histology: chondrocytes quantitation and size estimation in cartilage layer (Table 7).

Table 7. Quantity and size of chondrocytes in cartilage of children received (main group) and not received (control group) FQs therapy.

Cartilage	Chondrocyte count in 1 mm ²		Chondrocyte size in mcm	
	Treatment group	Control group	Treatment group	Control group
Superficial zone	404±15,2	156±13,6	0,7±0,5	0,6±0,3
Significance level	P < 0,01		P > 0,05	

As it is shown in the table 7 at the background of FQs use in superficial cartilage layer chondrocytes number of normal size is increased – hyperplastic reaction. One might recall an opposite pattern was found in experimental animals: declining number of chondrocytes and its shrinkage (dystrophic reaction).

Hyperplastic reaction in cartilage is not reparative in this case as it is usually occurred when necessary to close a defect, but cartilage damage was not found in our study. It is probable, that this reaction can be related to some nontoxic FQs accumulation in cartilage, and it is a unique «disturbance phenomenon» to their presence, i.e. FQs therapy is irritating rather than damaging factor.

As it is shown in the table 8, a joint cartilage only reliably accumulates its small amount during the prolonged FQs use, resulting in hyperplastic reaction (cumulative effect of FQs).

Table 8. Comparisons of total fluorine content at the different parts of right knee-joint in children who were treated with FQs for a long time (main group) and who were not treated with FQs (control group).

Group	Fluorine content in mcg		
	Cancellous bone	Growth plate	Cartilage
Control group	1485±133	1691±161	1289±77
Treatment group	1572±162	1864±225	1948±113
Significance level	P>0,05	P>0,05	P<0,05

So a cartilage in children along with chondrocytes (up to

10% by total weight of cartilage tissue), which have metabolic activity comparable to that of hepatocytes, seemingly are to present increased sensitivity to any exogenous damaging, for example, - FQs. But FQs being chondrotoxic in many immature animals do not have such side effects in children nor after single neither after repeated or continuous prolonged use.

4. Follow-up Phase II (Spontaneous Reports in 2006 – 2019)

4.1. Russian Data in Vigibase

As of 10-FEB-2019 there were only 0,02% reports of adverse reactions in children from Russia compiled in Vigibase, herewith there is no mention of FQs in these reports [9].

4.2. Russian Pharmacovigilance Service

Russian pharmacovigilance service had registered reports of 8 adverse events (AE) related to musculoskeletal system under CPF treatment for the period 2008 – 2018 (arthralgia, myalgia), however without age mention [10].

4.3. Local Data (University Hospital)

Our database for the period 2006 – 2019 includes 37 AE reports related to FQs (children at the age 9 months to 17 years), only 3 among them (8,1%) were related to QA: 2 cases were associated with levofloxacin use and one case – with pefloxacin treatment. As usual QA was fully reversible.

5. Discussion

First of all we would like to say that the term “quinolone arthropathy” used in the literature seems not fully accurate of this FQs-related side effect. Firstly, because of the fact that an active use of the first quinolone generation in due time (1962 – 1986), nalidixic acid, in particular, as an uroseptic agent in children (from 3 months old) and adolescents according to the studies of Shaad (1986) and Nuuntinen (1994), and our research [11, 12], was not followed by arthropathy development (unlike the experiments with animals). But fluorine atom attachment to the nalidixic acid molecule and other transformations [13] not only has increased antimicrobial activity, but dramatically has widened volume distribution, including diffusion rate into joint structures [14], which in some cases has resulted in arthropathy in children due to individual FQs intolerance.

Secondly, QA's external appearance looks like acute arthritis (pain, swelling, disability, fast reverse) but MRI and morphological exams show an inflammation involvement of synovial membrane only.

Thus considering the previous data and our data amorphous term “quinolone arthropathy” can be replaced by quite specific “fluoroquinolone arthritis (synovitis)”.

Nor weight-bearing nature of joints neither FQs treatment duration do not play any role (unlike the experiments with animals) in QA occurrence in children.

The only thing that matters is morphological and immunological synovial joint maturity which lets to react by inflammation after FQs use in isolated cases (children with relevant arthrological and/or allergic history).

However it should be noted that drug-related arthropathy is quite common [8, 15], not FQs only privilege.

Disability and growth stunting in experimental animals occur not due to arthrotoxicity itself but as a result of chondrotoxicity – a damage of cover cartilage and cartilage of growth plate by fluoroquinolones.

As it turned out in the process of our research though both cartilages accumulate some FQs amount, but remain undamaged, and the first and the only target of QA inflammation is synovium as aseptic synovitis.

However if quinolone arthropathy in laboratory animals is exclusively fluorotoxic and was revealed in total number of animals, in QA clinical presentation it is, firstly, selective, and secondly, has immunological (cytokine-related) origin.

An important and interesting response feature of musculoskeletal system in children under FQs treatment is absence (unlike adults) of ligaments and tendons damage: for 30 years of these AB use we have not observed such

complication, which suggest age-related character (only in the elderly) of the side effect.

So, joint cartilage and growth plate in children under prolonged FQs use are not damaged. From one side it can be explained by lower therapeutic doses of FQs than in experiment but also by genetic and species difference of human cartilage collagen and cartilage collagen of laboratory model and hence different sensitivity to drug effects [5].

Based on our research we concluded that joint cartilage and growth plate in children under prolonged FQs treatment did not damaged also because those drugs did not accumulate in chondrotoxic concentrations. It could be explained by chondroprotective synovial joint structure, self-protection of its triadic system: synovial membrane – synovial fluid – cartilage [4, 5].

Let us consider this protective mechanism using knee joint – the more frequent target under FQs use – as an example.

Joint cartilage has two sources of nutrition (and entry of foreign substances): synovial fluid which surrounds cartilage of joint surfaces and blood brought by capillaries on the part of subchondral bone. However, cover cartilage in children is hypovascular (our own data), in addition subchondral bone can limitedly accumulates FQs (Table 8) which significantly reduces its penetration to joint cartilage.

FQs diffusion from the synovial fluid into the cartilage is possible in principle, as:

1. Environment in the cartilage matrix is more acid than in the synovium (pH difference – 0,3), and FQs are acid-reacting compounds – quinolone carboxylic acid derivatives;
2. Joint cartilage contains some lipid amount (0,32 – 3,47 g/l) in main matrix and FQs are highly lipophilic substances. However, water content in a cartilage is so significant that it is customary to speak of its hyperhydrated state;
3. Besides FQs ingress from synovial fluid is hampered by synovium's barrier function as it is saturated and therefore viscous solution of hyaluronic acid which makes it difficult for small molecules to move (monofluoroquinolones have molecular weight < 500D).

Synovium's barrier function manifests itself in the fact that its alkaline reaction (pH 7,3 – 7,6) makes difficult acid-reacting FQs' movement in the blood-synovium direction (overcoming the hemo-synovial barrier).

4. There is other thing important. Along with the absorption joint system there is proprietary elimination system [16], which we call joint clearance – the possibility of metabolic products and xenobiotics removal from the cartilage through the microcirculatory pathways as in the direction of the subchondral bone vessels, as well as towards the articular cleft followed by their resorption by the synovial membrane. Reverse absorption is lower for high molecular weight substances. That is why FQs which are low molecular weight substances have a higher reverse absorption (joint clearance), and active and passive movements accelerate this process.

However, some FQs accumulation in joint cartilage still occurs at the expense of subchondral bone vessels, and it

responds to it by «disturbance phenomenon» - the hyperplastic reaction.

6. On the Role of the Synovial Membrane in the Nature of QA

Synovial membrane as a natural mechanical barrier: type A synovial cells having many of the characteristics of macrophages and structurally adapted for phagocytosis (accumulation, retention) actively absorb various substances (including xenobiotics) passing through the synovial membrane and prevent them from excessively penetrating further into the synovium and then into the cartilage [4, 17].

Synovial membrane as an immunological barrier: having in itself lymphocytes, mast and plasma cells synovial membrane actively responds in a number of cases (relevant arthrological and/or allergic history) to FQs presence (immunologically active compounds) by inflammatory reaction – aseptic allergic synovitis, keeping xenobiotics out of the joint cavity and the cartilage. This was shown in an interesting paper [7], where PF was not registered in the synovium at the background of the developed QA.

Thus, joint structures in children react in two ways during FQs treatment. QA is only an acute reaction (in some patients) to FQs of the synovial membrane to FQs, and always with reverse effect. Also, a cumulative chronic effect due to chondrotropicity of FQs appears in the form of a favorable clinically asymptomatic hyperplastic reaction - «disturbance phenomenon» - for the presence of xenobiotics.

7. Conclusion

The results of clinical investigations demonstrated that any dosing regimen of CPF and in particular OF results in minimal side effects but developing arthropathy has always acute course only and is drug-dependent and age-dependent: it appears in joints of synovial type mainly as a result of PF use in children of pubertal age only having usually allergological and/or arthrological history that helps us to distinguish this risk group for QA development.

Studies of joints morphology (not revealed cartilage injury), of annual rate of growth, follow-up observations and measurement of proinflammatory cytokines showed that arthropathy in children as a result of FQs administration – is independent (isolated) form of joints reaction on FQs in children different from one in experimental arm by mechanism of development and consequences.

Two clinical forms of FQs were identified – arthrological (only pain) and arthritic (pain, effusion, disability) that allows to optimize the NSAIDs dosing: simple analgetics for pain form and group of brufen for arthritic form until disappearance of joints symptoms.

Use of fluorine as a biomarker of FQ and determination of fluoride in osteochondrous tissue of right knee joint of patient with aplastic anemia and cystic fibrosis died from

progressive underlying disease allowed to determine low accumulation of FQ in different parts of joint that could explain absence of chondrotoxicity (disabled arthropathy and retardation of growth) in these patients.

One more particular reaction on FQs use in children identified in our investigations is absence of tendopathy despite of a part of patients with cystic fibrosis took prednisolone (in combination with FQs) that is confounding factor in adult patients.

The listed features of QA allow to consider it as benign drug-induced arthropathy in children and thereby prompting regulatory authorities to reconsider their objections to the application of FQs in children [18, 19].

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