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THERAPEUTIC ASPECTS OF FLUOROQUINOLONES CLINICAL ROLE IN PEDIATRICS

***Bangari Anil Kumar[1], T.Bhanu Chand[1], CH.Venkat Rao[1], K.Blessy Lavanya[1], V.P.Mahesh Kumar[2]**

[1]Internship, Doctor of Pharmacy, Department of Pharmacy Practice, Annamalai University.

[2]Associate Professor, Department of Pharmacy Practice, Annamalai University.

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***Correspondence for Author**
Bangari Anil Kumar
Internship, Doctor of Pharmacy, Department Of Pharmacy Practice, Annamalai University.

ABSTRACT

This study was aimed with an objective to review the pharmacokinetics and clinical indications of Fluoroquinolones in children.A MEDLINE search (January 1966–March 2013) was conducted for relevant literature.Data from published studies were reviewed for the assessment of pharmacokinetics, efficacy, and clinical indications of Fluoroquinolones in children.Fluoroquinolones were successfully used in immunocompromised children and also in those suffering from multidrug-resistant Gram-negative infections (including neonatal infections and multidrug-resistant enteric infections caused by Salmonella and Shigella spp).Fluoroquinolones have broad spectrum coverage of gram-positive and gram-negative bacteria, including Pseudomonas aeruginosa and intracellular organisms. Fluoroquinolones are well absorbed from the gastrointestinal tract, have excellent tissue penetration, low protein binding, and long elimination half-lives. Ciprofloxacin is the most frequently used. Fluoroquinolones in children used most often in the treatment of pulmonary infection in cystic fibrosis as well as salmonellosis and shigellosis. Other uses include chronic suppurative otitis media, meningitis, septicemia, and urinary tract infection. Fluoroquinolones are associated with tendinitis and reversible arthralgia in adults and children. The use of Fluoroquinolones in children has been restricted due to potential cartilage damage that occurred in research with immature animals. Fluoroquinolones although with limited safety data in pediatric population are used as mainstay for pulmonary infections in cystic fibrosis, Gram-negative neonatal meningitis, shigellosis and salmonellosis. Currently they are considered pediatrics as second-line antibiotics, and as alternative for other drug therapies when they do not show adequate

therapeutic effect. Many pneumococcal, staphylococcal strains are known to develop rapid resistance to them rendering them ineffective. The studies have been done to identify high rate of articular adverse effects in children treated with Fluoroquinolones, although this couldn't be established with firm evidence. Dosing recommendations for children need to be studied more extensively along with assessment of safety data.

KEY WORDS: Fluoroquinolones, pediatrics, cystic fibrosis, pharmacokinetics

I INTRODUCTION

The first ever quinolone used in antibiotic drug therapies was Nalidixic acid[1].After thatseveralamendmentsof Nalidixic acid have been made to enhance its antimicrobial,pharmacokinetic, and therapeutic properties. Fluoroquinolonesbeing derivative of quinolones with increased bactericidaleffect and activity against a wide spectrum ofgram-positive and gram-negative bacteria, such as *Pseudomonas aeruginosa* and other common microbes.[2],[3]Furthermore, most of these drugs are well absorbed from thegastrointestinal tract, have remarkable tissue permeation, long elimination half-lives, and low protein binding[4–6]Many of latest sold quinolones have an prolongedactionagainst gram-positive organisms (*e.g. Staphylococcus aureus,Streptococcus pneumonia, enterococci*) & anaerobesthat are resistant to ciprofloxacin and ofloxacin.[7–11]

Ii Mechanism Of Action

The quinolone antibiotics target bacterial DNA gyrase and topoisomerase IV. For numerousgram-positive bacteria, topoisomerase IV is the prime target. For many gram-negative bacteria, DNA gyrase is the primary quinolone target. They strongly inhibit the Type II enzymes responsible for the replication of double stranded DNA including DNA gyrase referred topoisomerase II and topoisomerase IV. The quinolones inhibitgyrase-mediated DNA supercoiling at concentrations that correlate well with their effective antibacterial actions (ref figure 1). Mutations of gyrA can confer resistance to these drugs. Topoisomerase IV splits catenated DNA molecules that result from DNA replication, and also is a target for quinolones.

Iii Spectrum Of Activity

Fluoroquinolones have a very good spectrum of activity. They are active againstseveral clinically important aerobic Gram negative bacilli like those belonging toenterobacteriaceae (eg *E coli*) and *Pseudomonas aeruginosa*. They are also activeagainst Gram positive cocci

like *S pneumoniae*, *S aureus* and beta hemolyticstreptococci. *H influenzae*, *Chlamydia pneumoniae*, *Mycoplasma pneumoniae*,*Legionella pneumoniae* are also susceptible [12, 13].Fluoroquinolones have been studied extensively in adultpopulations and have been found to be well tolerated andeffective in the treatment of various infections. [3, 14-15]Conversely, their use in children younger than 18 years of age hasbeen limited. The limitation for quinolones in children andadolescents is due to their probable risk to cause cartilagetoxicity& articular damage in joints in immature animals.Quinolones have been used in pediatric population,despite lack of their documented safety and tolerability for practice in infants and children.

Iv Pharmacokinetics Of Fluoroquinolones

Fluoroquinolones pharmacokinetic data in children are limited as a result of their limited use.This group of drugs is well absorbed from the gastrointestinal tract and all exceptnorfloxacin penetrate well into tissues. Newer Fluoroquinolones have better properties like longer serum half-life, higher peak levels, bioavailability and extensive tissue penetration [12] Because of intracellular penetration, they are useful for treating infections due to Mycobacteria and salmonella [12,13]. A recent study showed that the newer Fluoroquinolones, Gatifloxacin is swiftly absorbed in infants and children and permits once a day dosing [16]. Bioavailability ranges from 10-30% fornorfloxacin to 80-90% for ofloxacin [13]. Elimination is mostly through kidneys,unchanged.Studies indicate that systemic elimination is faster in children so larger dosesare obligatory [13].

Capparelli et al.[17] reported rapid absorption and faster clearance of single-dose Gatifloxacin in infants and children compared with adult patients and similar elimination half-life in older children to that of adults whereas a shorter half-life was revealed in patients of less than 6 years of age. Most pharmacological studies havebeen performed in older children with cystic fibrosiswithPseudomonas spp. infections and these have documentedthe necessity for higher than usual doses in this groupof patients. Two recent trials–one regarding chronic otitis media children undergoingplacement of tympanostomy tubes and the otherpatients with acute otitis media (AOM)–indicatedthat the concentration of levofloxacin in middle earfluid rapidly approximates plasma concentrations afterthe drug has been taken[18]. The pharmacokinetics of oral and intravenous ofloxacinhas been studied in 17 children (age 5–14 y) with typhoidfever [19]. The patients were randomized to receiveofloxacin 7.5 mg/kg orally followed by 7.5 mg/kg intravenouslyover 30 minutes in 7 patients or the same dose intravenouslyand

then orally in10 patients. The mean oral bioavailabilitywas 91%, which is analogous to that for healthy adultvolunteers. The mean $C_{max}$of ofloxacin was significantlyhigher ($p = 0.0008$) after a single intravenous dose (8.7mg/L) compared with a single oral dose (5.5 mg/L). The meant_{max}values following single intravenous and oral doseswere 0.5 and 1.69 hours, respectively. The mean apparentvolume of distribution after intravenous administrationwas 1.28 L/kg. The order of the route of administration (Intravenousfirst or PO first) had no significant effect on the C_{max}, t_{max}or AUC.

The pharmacokinetics of ciprofloxacin were studied in 16 children (7 infants, age 5–14 week; 9 children, age 1–5 y) after administration of a single oral dose (15 mg/kg) on an empty stomach[20]The oral mixture was prepared by grinding the tablet and mixing it with 50 Ml of water. Timed serum samples were taken during 12 hours after administration of the drug. The mean ± SD peak concentration (C_{max}) values in infants and children were 3.3 ± 1.3 and 2.1 ± 1.4 mg/L, respectively; time to reach C_{max}(t_{max}) was 1.18 ± 0.46 and 1.0 ± 0.25 hours, respectively. There were no differences in the C_{max}or t_{max}between the groups. The elimination half-life of ciprofloxacin was longer ($p < 0.001$) in infants than in children (2.73 ± 0.28 vs. 1.28 ± 0.52 h, respectively). Ciprofloxacin elimination half-life in children seems to be shorter than in adults (3– 5 h). The authors recommended increasing the frequency of oral ciprofloxacin to three times daily in children aged one to five years.

V Clinical Indications

The use of Fluoroquinolones in a child or adolescent is limited to special circumstances after careful assessment of the risks and benefits for the individual patient [21]. The main use of Fluoroquinolones in pediatrics should bereasonably in serious life-threatening infections for which other antibiotics therapies are not effective or available. Indications in children will include treatment of Infections caused by multidrug-resistant pathogens for which there is no safe or effective alternative or as second line where first line therapy has failed and Infections where no other effective oral agent is available and parenteral therapy is not feasible [21].

Further use of these drugs should be focusedto cystic fibrosis andImmune compromised patients and multidrug–resistant Gram-negative infections(including neonates), complicated urinary tract infections and multidrug-resistant enteric infections. Oral and topical quinolone therapy is highly effective in chronic otitis due to Pseudomonas spp [22]. The use of Fluoroquinolones in lower respiratory tract infections (LRTI) should be vigilant and restricted to patients that lack other therapeutic options.

Cystic Fibrosis

Combination parenteral therapy with an aminoglycoside and an antipseudomonal b-lactam is theStandard treatment for acute pulmonary exacerbation. However, parenteral therapy often requires hospitalization and relapse after treatment may necessitate maintenance therapy. Because of its good activity against P.aeruginosaand good oral bioavailability, ciprofloxacin has been used in the treatment of pulmonary infection in some adults with cystic fibrosis [23-27]. Ciprofloxacin is the most extensively studied Fluoroquinolones in patients with cystic fibrosis. It has been used for treatment of acute exacerbation of pulmonary infections and for maintenance therapy. Several studies of ciprofloxacin in children with cystic fibrosis have been published (Table 2). [28-30] Oral ciprofloxacin was shown to be as efficacious as a combination of β-lactams and aminoglycosides; the oral administration of the drug, thus making hospitalization unnecessary, contributed significantly to patients' quality of life. Therefore, cystic fibrosis is one of the conditions under which the agreement for use of Fluoroquinolones in children is unanimous

Typhoid and Paratyphoid Fevers

Oral ciprofloxacin and ofloxacin demonstrates clinical and bacteriological cure in children. Although their superiority over other drugs is not established. A Cochrane review [31] identified 33 trials of which 3 were exclusively in children. In adults, chloramphenicol was not significantly different from Fluoroquinolones in causing clinical or microbiological failure. In trials of hospitalized children, Fluoroquinolones were not significantly different from ceftriaxone (60 participants, 1 trial) or cefixime (82 participants, 1 trial). Norfloxacin had more clinical failures than other Fluoroquinolones (417 participants, 5 trials). Trials associating different durations of Fluoroquinolones treatment displayed no statistically significant differences (693 participants, 8 trials)

Immunocompromised Patients

Fluoroquinolones are not recommended currently as first line therapy in the treatment of infections in immunocompromised children or children on cancer chemotherapy with fever and neutropenia, but may be used for off label indications in difficult-to-treat infections. These compounds are possibly not superior to standard antibiotic combinations in children with febrile neutropenia [32], but the likelihood of oral administration and avoidance of hospitalization in selected low-risk children is striking[12].

Gastrointestinal Tract Infection

They are usually caused by multidrug-resistant *Salmonella* species (MDRS),*Shigella* species, *Vibrio cholerae* or *Campylobacter jejuni*. Occurrences of such strains have amplifiedsignificantly in recent years. Ciprofloxacin is clinically valuable and safe for GI infections in children [13]. It was used effectively in an epidemic of shigellosis [33].

Therapeutic preferences for MDRS comprise third-generation Cephalosporins [34-36]andFluoroquinolones [37].Thirdgeneration Cephalosporins are approved for use in children along with their excellent safety profile but however they are expensive and must be given parenterally. Therapeutic failure and relapse in MDRS have occurred with Cephalosporins, even when active in vitro [38, 39].Third-generation Cephalosporins were associated with relapse, failure and death in patients with Salmonella meningitis [40,41].In two comparative studies, ceftriaxone was less effective than ciprofloxacin[42]and ofloxacin[43]in the treatment of typhoid fever. Clinical response to cefotaxime was less favorable than that to ofloxacin [44].

Chronic Suppurative Otitis Media or Malignant Otitis Externa

Caused by *P.aeruginosa*,Oral or topical applications can be used. A Cochrane review [45] Identified 9 trials (842 analyzed participants or ears). It was revealed Topical quinolones were superior than systemic quinolone and non-quinolone antibiotics at clearing discharge at 1-2 weeks.Role of Fluoroquinolones in acute otitis media (AOM) is restricted. However, Gatifloxacin or Levofloxacin can be useful in treating complicated AOM failing to respond to initial antibiotic therapy [22].

Gram Negative Neonatal Sepsis/Meningitis

Fluoroquinolones penetrate well into the CSF in the presence of inflamed meninges and the CSF concentrations surpass the minimum inhibitory concentrations (MICs) for susceptible organisms [46, 47].The concentration of Fluoroquinolones in the CSF exceeded 50% of the serum concentration in the presence of inflamed meninges [47]. Sinceitshigh penetration intoCSF, cerebral tissues and action on Gram negative bacteria, it can be used fortreating Gram negative meningitis in the neonates. It is advocated that it decreaseschance of cerebral abscess formation in the neonates and the immunocompromised[13]. 116 neonates with microbiologically proven/probable sepsis were treatedeffectively with ciprofloxacin. No short term adverse events were observed. Noclinical arthropathy or growth impairment occurred at one year follow up [48].

Vi Tables & Figures

Table 1 Efficacy studies of Fluoroquinolones in Pediatric Population with GI infections

Reference	Type of Infection	No. Pts. (age, y)	Regimen	Clinical Outcome	Comments
Vinh et al. (1996)[61]	uncomplicated MDR typhoid fever	53 (2–14) 47 (1–14)	ofloxacin 15 mg/kg/d q12h for 2 d ofloxacin 15 mg/kg/d q12h for 3 d	47 cured without relapse; 6 clinical failures 1 relapse responded to 7-d treatment; 2 clinical failures	clinical response similar in both groups ($p > 0.2$)
Arora et al. (1992)[64]	severe MDR typhoid fever	85 (8 mo–10 y)	ciprofloxacin 20 mg/kg/d q12h for 10 d	all cured; no relapse	6 children had vomiting and received iv treatment for 1–2 d
Bavdekar et al. (1991)[63]	severe MDR typhoid fever	73 (1.5–18)	ciprofloxacin 10 mg/kg/d iv or 20 mg/kg/d po q12h[a]	all cured; no relapse	22% of pts. had life-threatening diseases
Dutta et al. (1993)[62]	severe MDR typhoid fever	18 (1.5–9.5)	ciprofloxacin 10 mg/kg/d q12h iv/po for 7–14 d after being afebrile	17 cured; no relapse	1 child died within 24 h from shock
Gendrel et al. (1993)[60]	severe invasive salmonellosis	7 (1.5–9.5)	pefloxacin 12 mg/kg/d po q12h for 7 d	all cured	1 relapse cured with another 7-d course
Rathore et al. (1996)[66]	MDR typhoid fever	55 (average 6.2)	ofloxacin dose unclear	all cured; no relapse	no long-term follow-up available
Sen et al. (1991)[67]	MDR typhoid fever	8 (2.5–13)	ciprofloxacin 15 mg/kg/d po q12h for 7–10 d	all cured; no relapse at 2-mo follow-up	pts. received ciprofloxacin after failure with other agents
El-Sherbini (1992)[57]	MDR typhoid fever	49 (2–5)	ofloxacin 50–200 mg po q12h for 7 d	96% cured	arthralgia in 4 pts. probably due to typhoid fever
Secmeer et al. (1997)[68]	typhoid fever	24 (<16)	ofloxacin 20 mg/kg po q12h for 10 d[b]	improvement by day 4 in all; all cured without relapse	ofloxacin produced shorter febrile duration ($p < 0.02$) and faster disappearance of symptoms ($p < 0.0028$) compared with TMP/SMX
		17 (<16)	TMP/SMX 10 mg/kg (TMP) q12h for 10 d[b]	improvement by day 4 in 65%; all cured without relapse	
Lolekha et al. (1991)[69]	shigellosis	25 (6 mo–13 y)	TMP/SMX 6 mg/kg/d (TMP) po q12h for 5 d	cure rate 100% with nalidixic acid and norfloxacin group; 64% with TMP/SMX ($p < 0.01$)	eradication of *Shigella* was faster with norfloxacin during the first 72 h ($p < 0.01$)
		30 (6 mo–13 y)	nalidixic acid 55 mg/kg/d q8h for 5 d		
		24 (6 mo–13 y)	norfloxacin 10–15 mg/kg/d po q12h for 5 d		
Guyon et al. (1994)[70]	MDR shigellosis	25 (8 mo–12 y)	pefloxacin 12 mg/kg po once daily for 3 d	all cured without relapse	84% eradication rate at 48 h; 100% at 7 d
	MDR shigellosis	13 (11 mo–13 y)	pefloxacin 20 mg/kg po single dose	all cured without relapse	stool was negative at day 3 and remained negative at days 5 and 8
Bhattacharya et al. (1997)[71]	shigellosis	27 (1–10)	nalidixic acid 60 mg/kg/d po q8h for 5 d	cure rate 100% with norfloxacin; 3 pts. in nalidixic acid group failed and responded to norfloxacin	norfloxacin recipients had shorter duration of diarrhea and blood in stool than pts. receiving nalidixic acid ($p < 0.05$)
		32 (1–10)	norfloxacin 20 mg/kg/d q12h for 5 d		

MDR = multidrug resistant; SMX = sulfamethoxazole; TMP = trimethoprim.
[a]Patients received either ciprofloxacin iv (55%) or po (45%). Ciprofloxacin was given alone in 10% of patients, combined with cefuroxime in 50% of patients, and combined with other agents (i.e., chloramphenicol, amoxicillin, TMP/SMX) in 22%.
[b]Patients received TMP/SMXfor TMP/SMX-susceptible strains, and ofloxacin for TMP/SMX-resistant strains.

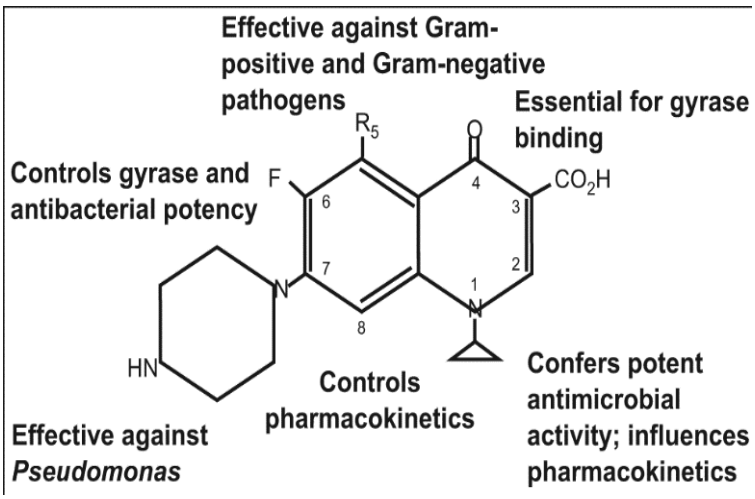

Figure 1 Mechanism of Action of Fluoroquinolones Structural activity Relationship

Vi Resistance – A Global health concern

Global surveillance studies demonstrate that Fluoroquinolones resistance rates increased in the past years in almost all bacterial species except *S. pneumoniae* and *H. influenzae*, causing community acquired respiratory tract infections. However, 10 to 30% of these isolates harbored first-step mutations conferring low level Fluoroquinolones resistance. Fluoroquinolones resistance increased in Enterobacteriaceae causing community acquired or healthcareassociated urinary tract infections and intraabdominal infections, exceeding 50% in some parts of the world, particularly inAsia. One to two-thirds of Enterobacteriaceae producing extended spectrum *β*-lactamases were Fluoroquinolones resistant too.Furthermore, Fluoroquinolones select for methicillin resistance in *Staphylococci*. *Neisseria gonorrhoeae* acquired Fluoroquinolones Resistance rapidly; actual resistance rates are highly variable and can be as high as almost 100%, particularly in Asia, whereasresistance rates in Europe and North America range from <10% in rural areas to >30% in established sexual networks. In general,the continued increase in Fluoroquinolones resistance affects patient management and necessitates changes in some guidelines, forexample, treatment of urinary tract, intra-abdominal, skin and skin structure infections, and traveller's diarrhea, or even precludesthe use in indications like sexually transmitted diseases and enteric fever [49].

VII CONCLUSION

Fluoroquinolones although with limited safety data in pediatric population are used as mainstay for pulmonary infections in cystic fibrosis, Gram-negative neonatal meningitis, shigellosis and salmonellosis. Currently they are considered pediatrics as second-line antibiotics, and as alternative for other drug therapies when they do not show adequate

therapeutic effect. They must be used very judiciously since they can enhance the multidrug resistance in various bacterial strains. Many pneumococcal, staphylococcal strains are known to develop rapid resistance to them rendering them ineffective. The studies have been done to identify high rate of articular adverse effects in children treated with Fluoroquinolones, although this couldn't be established with firm evidence. Dosing recommendations for children need to be studied more extensively along with assessment of safety data.

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