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Fluoroquinolones-A New Definition of Antibiotics

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Abstract

Fluoroquinolones have been regarded as the latest class of antibacterials derived from the synthetic origins possessing broader spectrum of bactericidal activity. They were first discovered in early 1960s but introduced as antibacterials in 1986. These drugs fall in to four generations. Chemically they are modified quinolones. The first generation quinolones were widely used, pertaining to their suitability in oral application, for the treatment of serious infections caused by gram (-) ve organisms including pseudomonas. The current fourth generations, fluoroquinolones have got splendid areas of chemical chemotherapy against varieties of afflictions etiologically induced by gram (+) ve and gram (-) ve bacteria, aerobic and anaerobic microorganisms even significantly in community acquired pneumonia, intra abdominal infections as well.

1. Introduction

The evolution of quinolones actually originated from the discovery of nalidixic acid in 1962 as a by-product of antimalarial research it is the first representative of the quinolones effective against some Gram-negative microbes.[1] Nalidixic acid became the lead compound for medicinal chemists for structural modifications to get many newer fluoroquinolones in order to getrid of its three major shortcomings are narrow spectrum covering Gram (-ve) organisms, achieves inadequate tissue levels for systematic infections and bacterial resistance development.[2]

This opened the flood gate for synthesizing newer and more interesting fluoroquinolones.[3] Out of more than 8000 analogues of fluoroquinolones synthesized bearing variety of ring systems, a few dozens have been established in the market, and more are in the horizon to be introduced.[4] Such an explosive growth of this group of compounds occurred mainly due to three factors; firstly, an unprecedented mode of action depending on inhibition ability of susceptible micro-organisms to shape their DNA for storage or replication; secondly, their potency and antimicrobial spectrum being equally comparative to the desired fermentation-based semi-synthetic antibiotics; and finally, their chemical structure being simple, a large number of analogues could be prepared following simple synthetic sequences in a cheaper way from readily available intermediates.

Further, rapid progress has been made towards broadening their spectrum of activity based on structure-activity relationship (SAR) to treat various systemic infections other than that of urinary tract infections (UTI) [5], improving their pharmacokinetic properties [6] and to reduce adverse reactions, especially central nervous system (CNS) side effects; which is common among these group of compounds.

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2. Classification

Classifications are of the following types: Table 1 and 2.

3. Mechanism of Action

The bactericidal effects of fluoroquinolones like earlier quinolones are mediated through their ability to block activity of bacterial DNA gyrase enzyme system. The function of this enzyme is to enable the long bacterial DNA to fit into the cell through supercoiling. In linear as well as circular DNA, the two strands of polynucleotides are coiled around each other so as to form a double helix.[7] There are approximately 10 base pairs per turn of helix. Every time one of the strands of DNA winds with each other and makes a link. Thus a circular DNA containing several base pairs is expected to contain about 500 links. When such a number in a molecule is less than 500, the molecule becomes strained. To relieve the strain it supercoils and results in further coiling making a supercoiled structure.[8] The supercoiled DNA occupies less space than the relaxed DNA. In cells and in microorganisms enzymes topoisomerases control super coiling e.g. Gyrase. The inactivation of gyrase kills the bacterial cell by distrupting the DNA supercoiling so that DNA can no longer be contained within the cell and it bursts. The DNA gyrase is composed of two subunits A & B. A is coded with gyrase A gene and has the molecular size of 9700 daltons.[9]

The sub unit B has a molecular size of 89,835 daltons and is coded by the gyr B gene. The effect of quinolones on DNA replicative enzymes in mammalian cells and molecular mechanism of inhibition of DNA gyrase by such agents have been investigated extensively.[10] Quinolones bind co-operatively to DNA gyrase-induced specific sites on relaxed DNA. These investigations revealed that quinolones do not bind to DNA gyrase at their inhibitory concentrations rather conjugate preferentially to single-stranded DNA.[11] This showed that quinolones bind poorly to relaxed double stranded DNA but specifically to a saturable site on supercoiled DNA in a highly co-operative manner and such

Table: 1. On the basis of chemical composition of fluoroquinolones

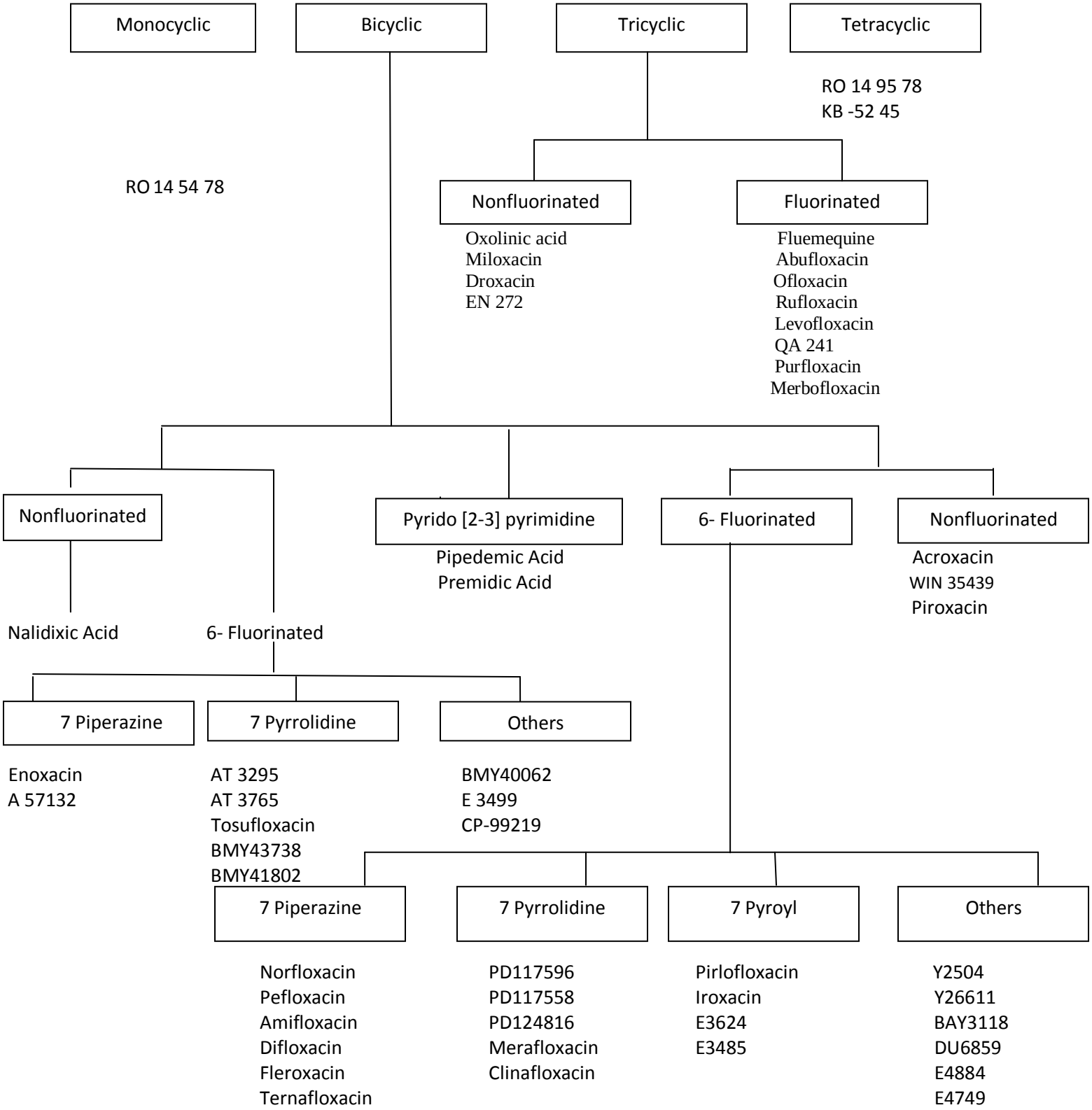
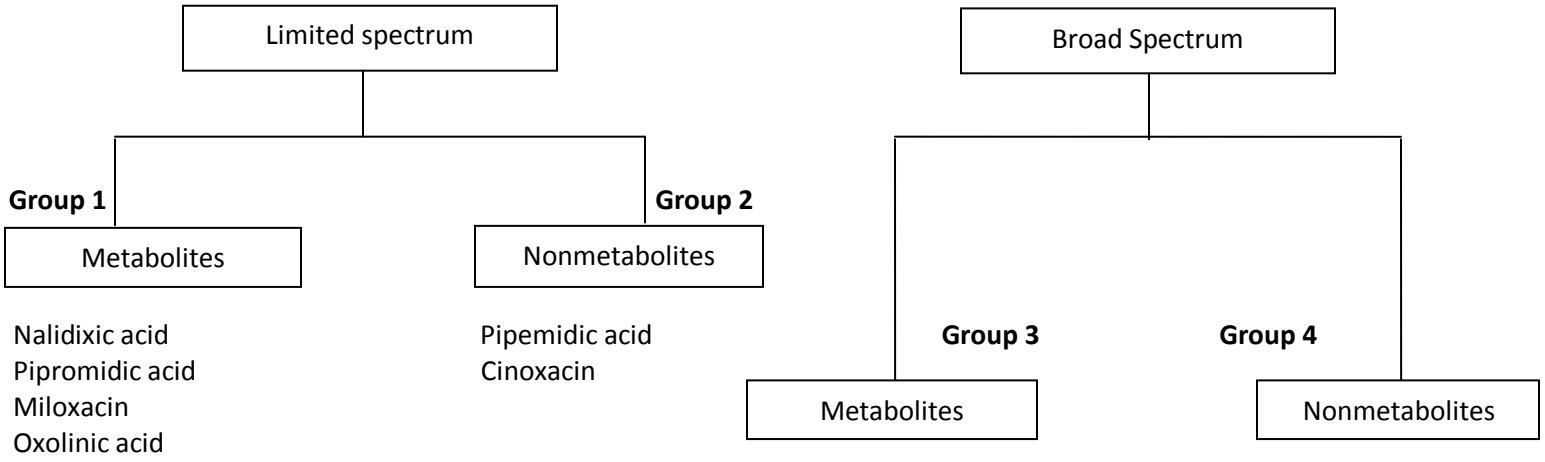


Table: 2. On the basis of Biological properties of fluoroquinolones



binding to relaxed double stranded DNA is enhanced by DNA gyrase. They are bactericidal at concentrations above MIC. The bactericidal action of older quinolones such as nalidixic acid was inhibited by the simultaneous addition of rifampin suggesting that protein synthesis was a requirement for bactericidal action for E. coli even in presence of rifampin or chloramphenicol.[12] It was also concluded that these compounds were bactericidal for non-dividing cells also. New quinolones such as ciprofloxacin is less active against Gr (+ve) than against Gr (– ve) bacteria suggesting the bactericidal mechanism of ciprofloxacin against Gram (+ve) and Gr (-ve) bacterial cell is different. This difference in mechanisms may be the attributed to inability of ciprofloxacin to achieve bactericidal cure in Staphylococcal infections.[13]

Therefore, it appears that some of the newer fluoroquinolones like sparfloxacin, tosufloxacin, lomefloxacin etc. also damage the bacterial cell memberane which leads to loss of cell contents. This unique mode of action of newer fluoroquinolones is mainly responsible for infrequent occurrence of bacterial resistance to this drugs.[14]

Currently it is established that the mode of action of quinolones involves interaction with both DNA gyrase, (the originally recognised drug target) and topoisomerase IV (a related type II topoisomerase). In a bacterial cell, these two enzymes often differ in their relative sensitivities to many quinolones and commonly DNA gyrase is more sensitive to Gram (-ve) bacteria while topoisomerase IV is more sensitive in Gram (+ve) bacteria.[15] Usually the more sensitive enzyme represents the primary drug target determined by genetic tests with poorly understood exceptions. X-ray crystallographic studies of a fragment of the gyrase A subunit as well as of yeast topoisomerase IV have revealed domains that likely include DNA and quinolone.[16]

The inhibition of DNA synthesis by quinolones requires the targeted topoisomerase to have DNA cleavage capability and collisions of replication forks with reversible quinolone DNA topoisomerase complexes convert them to irreversible forms. However the molecular factors subsequently generating DNA doublestrand breaks from irreversible complexes and that probably initiate cell death.[17]

4. Clinically Uses of Fluoroquinolones

Fluoroquinolones (other than moxifloxacin, which achieves relatively low urinary levels) are effective in urinary tract infections even when caused by multidrug-resistant bacteria, eg, pseudomonas.[18] These agents are also effective for bacterial diarrhea caused by shigella, salmonella, toxigenic E coli, and campylobacter. Fluoroquinolones (except norfloxacin, which does not achieve adequate systemic concentrations) have been used in infections of soft tissues, bones, and joints and in intra-abdominal and respiratory tract infections, including those caused by multidrug-resistant organisms such as pseudomonas and enterobacter.[19] Ciprofloxacin is a drug of choice for prophylaxis and treatment of anthrax, although the newer fluoroquinolones are active in vitro and very likely in vivo as well.[20]

Ciprofloxacin and levofloxacin are effective for gonococcal infection, including disseminated disease and chlamydial urethritis or cervicitis.[21] Ciprofloxacin, levofloxacin, or moxifloxacin is occasionally used for treatment of tuberculosis and atypical mycobacterial infections.[22] They may be suitable for eradication of meningococci from carriers or for prophylaxis of infection in neutropenic patients.[23]

Levofloxacin, gatifloxacin, gemifloxacin, and moxifloxacin are called respiratory fluoroquinolones, with their enhanced gram-positive activity against atypical pneumonia agents (eg, chlamydia, mycoplasma, and legionella), are effective and used increasingly for treatment of upper and lower respiratory tract infections.[24]

5. Pharmacokinetic Properties of Fluoroquinolones

After oral administration, the fluoroquinolones are well absorbed (bioavailability of 80–95%) and distributed widely in body fluids and tissues (Table 1). Serum half-lives range from 3 to 10 hours. The relatively long half-lives of levofloxacin, gemifloxacin gatifloxacin, and moxifloxacin permit once-daily dosing. Oral absorption is impaired by divalent cations, including those in antacids. Serum concentrations of intravenously administered drug are similar to those of orally administered drug. Most fluoroquinolones are eliminated by renal mechanisms, either tubular secretion or glomerular filtration (Table 1). Dose adjustment is required for patients with creatinine clearances less than 50 ml/min, the exact adjustment depending on the degree of renal impairment and the specific fluoroquinolone being used. Dose adjustment for renal failure is not necessary for moxifloxacin. Nonrenally cleared fluoroquinolones are relatively contraindicated in patients with hepatic failure.[25]

S.N.	Drug	Half Life (Hr.)	Oral Bioavailability	Peak Serum Conc. (G/Ml	Oral Dose (Mg)	Primary Route of Excretion
1	Ciprofloxacin	3-5	70	2.4	500	Renal
2	Gatifloxacin	8	98	3.4	400	Renal
3	Gemifloxacin	8	70	1.6	320	Renal & nonrenal
4	Levofloxacin	5–7	95	5.7	500	Renal
5	Lomefloxacin	8	95	2.8	400	Renal
6	Moxifloxacin	9–10	> 85	3.1	400	Nonrenal
7	Ofloxacin	5–7	95	2.9	400	Renal
8	Norfloxacin	3.5–5	80	1.5	400	Renal

6. Resistance

During fluoroquinolone therapy, resistant organisms emerge about once in 107–109, especially among staphylococci, pseudomonas, and serratia.[26] Resistance is due to one or more point mutations in the quinolone binding region of the target enzyme or to a change in the

permeability of the organism. Resistance to one fluoroquinolone, particularly if it is of high level, generally confers cross-resistance to all other members of this class.[27]

7. Adverse Effects

Fluoroquinolones are extremely well tolerated. The most common effects are nausea, vomiting, and diarrhea. Occasionally, headache, dizziness, insomnia, skin rash, or abnormal liver function tests develop.[28] Photosensitivity has been reported with lomefloxacin and pefloxacin. QTc prolongation may occur with gatifloxacin, levofloxacin, gemifloxacin, and moxifloxacin.[29] Ideally, these agents should be avoided or used with caution in patients with known QTc interval prolongation or uncorrected hypokalemia; in those receiving class IA (eg, quinidine or procainamide) or class III antiarrhythmic agents (sotalol, ibutilide, amiodarone); and in patients receiving other agents known to increase the QTc interval (eg, erythromycin, tricyclic antidepressants).[30] Gatifloxacin has been associated with hyperglycemia in diabetic patients and with hypoglycemia in patients also receiving oral hypoglycemic agents. Because of these serious effects (including some fatalities), gatifloxacin was withdrawn from sales in the USA in 2006; it may be available elsewhere.[31, 32]

Fluoroquinolones may damage growing cartilage and cause an arthropathy.[33] Thus, these drugs are not routinely recommended for patients under 18 years of age.[34] However, the arthropathy is reversible, and there is a growing consensus that fluoroquinolones may be used in children in some cases (eg, for treatment of pseudomonal infections in patients with cystic fibrosis).[35] Tendinitis, a rare complication that has been reported in adults, is potentially more serious because of the risk of tendon rupture.[36] They should be avoided during pregnancy in the absence of specific data documenting their safety.[37]

8. Conclusion

Fluoroquinolones are the fastest growing antibacterial class in terms of global revenue. Fluoroquinolones development is based on structure activity relationship while pointing out to their mode of action. However, increased indiscriminate prescribing has led to recent occasional emergence of fluoroquinolone resistant bacteria. The new fluoroquinolones offer once daily dosing and a spectrum of activity different from that of existing fluoroquinolones. These differences should be placed in the context of local epidemiology, antibiotic resistance profiles and patterns of antibiotics. Consideration of the newer fluoroquinolones for a hospital or provincial formulary should take into account the potential economic advantages with respect to dosing, acquisition cost and adverse effects as well as potential for overuse of this class of agents. The new fluoroquinolones offer a useful addition to our current armamentarium of antibiotics for the institutional and community management of infections. The fluoroquinolone class of antimicrobial agents is being increasingly used empirically as resistance has developed to the more traditional antimicrobial agents. Evidence is mounting that suggests a link between inappropriate fluoroquinolone use, development of antimicrobial resistance against the entire fluoroquinolone class, and clinical failure. To maintain the activity of the fluoroquinolone class, clinicians need to implement an evidence-based approach to antimicrobial selection, particularly a strategy in which the most pharmacodynamically potent fluoroquinolone is matched, on an empiric basis when required, to anticipated bacterial pathogens.

Traditional reporting of susceptibility data may be misleading and may not readily identify initial changes in resistance patterns or differences between agents of the same class. To preserve fluoroquinolone activity, the activity of these agents must be continually assessed, and these agents must be used appropriately. The individual attributes of a given drug should be matched with the likely pathogen at specific infective sites. Expecting a single fluoroquinolone to be suitable for all infections is unreasonable, and excessive use of any single fluoroquinolone for all indications will lead to resistance that will adversely affect the entire class.

Given the defined strategy of selecting the agent with the best pharmacokinetic and pharmacodynamic profile against the known or suspected pathogen, an appropriate therapeutic choice for most serious infections, such as nosocomial pneumonia in which *P. aeruginosa* is a known or suspected pathogen, would currently include ciprofloxacin in combination with an antipseudomonal β-lactam or an aminoglycoside antibiotic. Ciprofloxacin, levofloxacin, and gatifloxain all achieve high concentrations in urine; thus, they would all be appropriate choices for treating urinary tract infections in the community. Ciprofloxacin would be the most appropriate therapy in cases where *P. aeruginosa* is a known or suspected pathogen. For other gram-negative infections, levofloxacin or gatifloxacin should be prescribed in appropriate doses to surpass the mutant prevention concentrations at the infection site.

For infections in which *S. pneumoniae* is anticipated to be the most likely pathogen (e.g., community-acquired pneumonia), moxifloxacin, which currently has the best antipneumococcal pharmacodynamic activity and the lowest mutant prevention concentrations against this organism. The targeted strategy proposed in this review is being implemented in a variety of institutions since the introduction of the third-generation fluoroquinolones. Due to these reasons, fluoroquinolones have been increasingly used in the recent past. But care must be taken while prescribing the dose and the dosage regime so that the micro-organisms do not develop resistance to fluoroquinolones also.

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