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The Future of the Quinolones

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Abstract

This review emphasises the advances in the development of newer quinolones: their broader antimicrobial activity particularly their increased activity against Pneumococcus and anaerobes; their longer half-life and tissue penetration including activity in cerebrospinal fluid; and their excellent efficacy in respiratory, intra-abdominal, pelvic, and skin and soft tissue infections. Also, considerable progress has been made in our understanding of the development of bacterial resistance to the newer quinolones. Additional advances in quinolone development are likely to provide better compounds for clinical use.

The future of a specific class of therapeutic agents is difficult to predict because a number of factors may determine the continued clinical utility of compounds in the class. Major factors that are likely to determine a successful future for a specific class of therapeutic agents include the development of newer compounds that have, relative to earlier compounds in that class:

- greater clinical efficacy
- less toxicity and greater safety
- lower propensity to induce resistance
- easier patient compliance
- shorter effective durations of therapy
- better cost-benefit ratio.

Although predictions are difficult, some estimates can be attempted if they are based on our previous experiences as well as current studies in progress. We are, in fact, in a better position now than we were a decade ago when the future prospects of the quinolones were first reviewed[1] and subsequently updated.[2,3] Substantial progress has been made recently in the development of newer quinolone agents, primarily because of advances in our understanding of the chemistry, the molecular mechanisms of quinolone action on various organisms, and the factors that lead to the development of quinolone resistance.

The first and key discovery was the identification of the enzyme DNA gyrase or topoisomerase II by Gellert and colleagues,[4] which led to a better understanding of the molecular basis for the potent antibacterial effects of the newer quinolones. We now know that there are 4 DNA topoisomerases in bacteria. Of these, topoisomerases I and III are not very sensitive to inhibition by the quinolones. In contrast, topoisomerase II and IV are the 2 major targets of the fluoroquinolones. The mechanism of action of the quinolones is that they inhibit DNA topoisomerases (gyrases), 4 subunits of which (2 A monomers and 2 B monomers) have been identified in topoisomerase II.[5,6] Topoisomerase II supercoils strands of bacterial DNA in the bacterial cell.[7,8] Each chromosomal domain is transiently nicked during supercoiling, which results in single-stranded DNA. When supercoiling is complete, the single-stranded DNA state is abolished by an enzyme that seals the nicked DNA. Thus, topoisomerase II (nicking-closing enzyme) nicks double-stranded DNA, introduces negative supercoils, and seals the nicked DNA.[4,9-12]

The second major advance contributing to the rapid expansion of the newer quinolones was the ability to chemically manipulate the nucleus of the 4-quinolones.[13-16] The basic molecule has been modified at the N-1 position, with different groups added to the C-6, C-7, and C-8 positions. These modifications result in major changes in the antimicrobial activity, pharmacokinetics and metabolic properties of the quinolones. Specific changes include the following: the addition of a fluorine atom at position C-6, which enhances DNA gyrase inhibitory activity and provides activity against staphylococci; addition of a second fluorine group at position C-8, which results in increased absorption and a longer half-life; addition of a piperazine group at position C-7, which provides the best Gram-negative activity; ring alkylation improves Gram-positive activity and half-life;[15] substitution of a methyl group for the piperazine group, which results in increased absorption and a longer half-life; and addition of a cyclopropyl group at position N-1, an amino group at position C-5, and a fluorine group at C-8, which

results in increased activity against *Mycoplasma* and *Chlamydia*. Similarly, adding a fluorine or chlorine at C-8 in combination with an N-1 cyclopropyl further enhances antibacterial activity.[15,16]

1. Microbiology

Early *in vitro* studies of the initial group of newer quinolones indicated that these compounds were:[2,17]

- very active against enteric Gram-negative aerobic bacteria and generally active against other aerobic Gram-negative organisms
- moderately active against *Pseudomonas aeruginosa* (ciprofloxacin was most active) and active against staphylococci, but with the potential for the development of resistance by these organisms
- only moderately active against streptococci, especially *Streptococcus pneumoniae*.

Thus, the development of resistance became a major concern during our early clinical experience, even though the spontaneous single-step mutation frequency for the newer quinolones was 1000-fold less than for nalidixic acid. Additional studies indicate that mutations in the *gyr*A gene of topoisomerase II in clinical isolates of *Staphylococcus aureus* confer resistance to the quinolones. Similar results have been found for *P. aeruginosa*, *Escherichia coli*, *Neisseria gonorrhoeae*, *Klebsiella* and *Citrobacter freundii*.[14,18] Resistance to the quinolones can also result from changes in quinolone permeation. Genes (*nfx*B and *cfx*B) that decrease the expression of the outer membrane protein OmpF at the post-transcriptional level decrease the accumulation of norfloxacin in cells, and porin-deficient bacterial mutants become more resistant to quinolones.[19,20] Recent advances in the development of the newest quinolones indicate that some of these have activity against quinolone-resistant bacteria.[16] Potent activity against quinolone-resistant strains, (particularly quinolone-resistant *S. aureus* and *P. aeruginosa*) is exhibited by the newest quinolones, clinafloxacin and sitafloxacin (DU-6859A), which have a C-8 chlorine atom.[16,21] Also, the newer quinolones with a C-8 methoxy group have improved activity against quinolone-resistant *S. aureus*.[22-25] Furthermore, some of the newest quinolones [trovafloxacin, sitafloxacin, clinafloxacin, moxifloxacin (BAY-128039) and gemifloxacin (SB-265805)] have enhanced activity against *S. pneumoniae* and anaerobes.[16,26-29]

2. Pharmacokinetics

Important and practical pharmacological aspects of the newer quinolones include excellent oral absorption, good tissue distribution with excellent interstitial fluid concentrations, significant entry into phagocytic cells, and excellent urinary concentrations after oral administration.[30] Advances in our understanding of structure-activity relationships has improved the pharmacokinetics (longer half-life and tissue penetration appropriate for once-daily administration) of some of the newest quinolones, including grepafloxacin, sparfloxacin, trovafloxacin, moxifloxacin, gatifloxacin, gemifloxacin and sitafloxacin.[15,16,31]

3. Clinical Uses

Many infectious diseases can be treated successfully with oral quinolone therapy. Specifically, bacterial infections of the respiratory tract (bacterial exacerbation of chronic bronchitis and pneumonia), urinary tract (uncomplicated and complicated), skin, soft tissues, bones and joints respond well to oral quinolones. Gastrointestinal infections, particularly infectious diarrhoea caused by toxigenic *E. coli*, *Salmonella* (including typhoid and paratyphoid fevers, and the chronic *Salmonella* carrier state), *Shigella*, *Campylobacter*, *Aeromonas* and *Vibrio* species, as well as by *Plesiomonas shigelloides*, are also highly responsive to oral quinolone therapy. In addition, some sexually transmitted diseases (gonococcal, chlamydial and chancroid infections) and pelvic infections can be cured with oral quinolone therapy.[32,33]

More recent clinical investigations with some of the newest quinolones, particularly trovafloxacin, have demonstrated excellent efficacy in intra-abdominal infections, in some postoperative surgical abdominal infections, as well as certain obstetrical/gynaecological infections, because of the anti-anaerobic (including *Bacteroides fragilis*) spectrum of activity. Also, trovafloxacin has been shown to be highly efficacious in the treatment of meningococcal meningitis. Thus, this is the first of the newest quinolones to demonstrate excellent penetration through the blood-brain barrier and clinical efficacy in a most serious infectious disease.[34] In addition, during the past decade we have accumulated much more clinical experience in the utility of newer quinolones in the treatment and prevention of infections in immunocompromised patients.[35]

4. Adverse Events

Toxicities with the early quinolones were low. Compared with other commonly used antimicrobial agents, the fluoroquinolones can be considered to be relatively well tolerated.[13,15,36] The commonest adverse events involve the gastrointestinal tract and the central nervous system (CNS). Gastrointestinal disturbances (anorexia, nausea, diarrhoea, vomiting, dyspepsia and

abdominal discomfort) are the adverse reactions reported most frequently (2 to 11%). CNS reactions (1 to 7%) may occur in the form of headache, dizziness, tiredness, vertigo, syncope, restlessness, insomnia, tinnitus and sensory changes.[13,15,36] Severe neurotoxic reactions are rare (<0.5%) and include psychotic reactions, hallucinations, depression and grand mal seizures, which are reversible with cessation of therapy. These direct CNS effects correlate roughly with quinolone binding at $GABA_A$ (γ-aminobutyrate) receptors in the brain, blocking GABA and leading to CNS stimulation.[15] Hypersensitivity reactions also are rare (0.4 to 2%) and include erythema, pruritus, urticaria, and rash. Equally rare are episodes of hypotension, tachycardia, nephrotoxic reactions (crystalluria) with elevated serum creatinine levels, thrombocytopenia, leukopenia, and anaemia. Transient elevations in liver enzymes have rarely been observed.[36]

51 cases of serious hepatic events, but no deaths, were reported during the postmarketing surveillance period for trovafloxacin when 1.2 million patients were treated, representing an incidence of less than 0.004%. Two newer quinolones, sparfloxacin and grepafloxacin, are associated with prolongation of the electrocardiographic QT_c (corrected QT) interval.

Moderate to severe phototoxicity, manifested by an exaggerated sunburn reaction, has been observed in patients who are exposed to direct sunlight while receiving some members of the quinolone class of drugs, such as lomefloxacin, fleroxacin, sparfloxacin, enoxacin and pefloxacin. Quinolones accumulating in high concentrations in skin have a higher risk of producing phototoxicity.[13,15]

Quinolone-associated arthropathy is a potential adverse reaction in humans. Substantial experience with the use of quinolones in children indicate little evidence of quinolone-induced arthropathy in humans.[15,36,37] Quinolones should be avoided during pregnancy and in nursing mothers because some are excreted into breast milk[38] and their safety has not been established.

Some fluoroquinolones show dose-dependent interactions with aluminum- or magnesium-containing antacids, so that simultaneous oral administration should be avoided. Interactions between some of the early fluoroquinolones and theophylline or caffeine have also been observed.[13,36]

The quinolones may interact to varying degrees with other drugs, including warfarin, H_2 receptor antagonists, cyclosporin, rifampicin (rifampin) and nonsteroidal anti-inflammatory drugs (NSAIDs). The concomitant administration of an NSAID with a quinolone may increase the risk of CNS stimulation and convulsive seizures.[13,36]

Disturbances of blood glucose, including symptomatic hyper- or hypoglycaemia, have been reported, usually in diabetic patients receiving concomitant treatment with an oral hypoglycaemic agent or insulin.[13,36]

5. Current Status

Many new quinolones have been synthesised during the past decade. Some offer important advantages over compounds developed earlier. Currently available newer quinolones, with their dates of approval for clinical use in the US, include norfloxacin (1986), ciprofloxacin (1987), ofloxacin (1991), temafloxacin (1992), which was withdrawn in 1992 because of toxicity, enoxacin (1992), lomefloxacin (1992), sparfloxacin (1996), levofloxacin (1996), grepafloxacin (1997) and trovafloxacin (1997). Quinolones that are not approved for clinical use in the US but are available in other countries include pefloxacin, fleroxacin and tosufloxacin.

In addition, a number of newer quinolones are in various phases of clinical investigation. These include rufloxacin, pazufloxacin, gatifloxacin, clinafloxacin, sitafloxacin, moxifloxacin and gemifloxacin. There are also other new quinolones that are in various stages of early development, such as prulifloxacin (PD-140288), nadifloxacin, balofloxacin, CFC-222, CS-940, HSR-903, CG-5501, and DW-116.[16,39-41] A new subclass of quinolones is also under early investigation. Compounds in this subclass, which include BMS-284756 (T-3811) among others,[42] are desfluorinated so that the fundamental C-6 fluorine is replaced, most often by an amino radical, which produces an aminoquinolone group of compounds.[42] Clearly, this list of new compounds is likely to be incomplete.

At the present time, it seems prudent to classify the quinolones into generations in a manner similar to the prior classification of generations of cephalosporins. There are a number of ways to categorise quinolones, for example by their chemical structure, by structure-activity relationships, by specific *in vitro* spectrum of antimicrobial activity, or by clinical efficacy. Such classifications are clearly arbitrary. Thus, the classification which appears in table I is based on potency and most recent spectrum of antibacterial activity against 'problem' bacterial organisms. This definition was selected because it is in keeping with the classification of cephalosporins into generations.[43] A uniform classification of quinolone generations is likely to be specifically defined in the near future (table I).

6. Future Developments

The future prospects of the quinolones, as outlined in earlier reviews,[2,3,43] suggested that newer compounds would be developed that would have: (i) greater potency; (ii) less frequent selection of resistance; (iii) better CNS/cerebrospinal fluid penetration; (iv) better patient safety and tolerability; (v) greater activity against Gram-positive bacteria, particularly staphylococci, pneumococci and *Legionella*; (vi) effectiveness against atypical organisms such as *Mycoplasma pneumoniae* and *Chlamydia pneumoniae*; and (vii) activity against anaerobes.[2,3]

Significant progress has been made recently, particularly with the introduction into clinical use of the very newest quinolones, especially trovafloxacin.[44-47] This quinolone has excellent activity against Gram-positive organisms, i.e. staphylococci and pneumococci (including high-level penicillin-resistant pneumococci), against 'atypical' organisms, i.e. *Mycoplasma* and *Chlamydia*, against *Legionella* and against anaerobes, including *B. fragilis*, and penetrates the CNS and cerebrospinal fluid better than earlier quinolones. Trovafloxacin has been shown to be highly effective in the treatment of epidemic meningococcal meningitis in Africa.[34] Thus, many of the earlier predictions have been accomplished by innovative manipulations of the basic chemical nucleus that have led to newer and more broadly effective compounds. In addition, newer compounds, some already approved for clinical use and others that should soon be approved, have better pharmacokinetics and pharmacodynamics, with longer half-lives that allow once-daily administration.[15,16]

Although much progress has been made, future research is likely to lead to even better compounds that have lower incidences of adverse reactions and serious toxicity. Current intense investigations into the mechanisms responsible for the development of resistance, particularly pneumococcal and staphylococcal resistance, which occurs with the induction of amino-acid changes in the *par*C and *par*E genes of topoisomerase IV (in pneumococci) and in *gyr*A genes (in staphylococci) are likely to lead to improved compounds for the treatment of infections caused by these bacteria in the near future. The results of these studies are likely to produce compounds that are more resistant to the rapid development of resistance.[48-54]

Furthermore, newer quinolones are likely to be approved for use in paediatrics, an indication that is long overdue.[55] In this context, as well as in adult patients, quinolones will ultimately be approved for the treatment of bacterial meningitis.

Also, new compounds used alone or in combination with other agents may provide more effective killing or may lower the risk of the development of bacterial resistance. In addition, the interactions of the quinolones with other antimicrobial agents may lead to synergistic or additive activity.[56,57] Antagonist activity is unlikely because of the unique mechanism of action of the quinolones.

Finally, additional progress in our understanding of the importance of structure-activity relationships should lead to the development of compounds that will accomplish all of the aforementioned needs as well as resulting in minimal adverse reactions and a lower rate of serious adverse effects, thus being as safe as possible for use in our patients.

Table I. Classification of quinolones

First generation	Third generation[b]
Nalidixic acid	Sparfloxacin
Oxolonic acid	Tosufloxacin
Cinoxacin	Gatifloxacin
Piromedic acid	Pazufloxacin
Pipemedic acid	Grepafloxacin
Flumequine	
Second generation	Fourth generation[c]
Norfloxacin	Trovafloxacin
Ciprofloxacin[a]	Clinafloxacin
Enoxacin	Sitafloxacin (Du-6859a)
Fleroxacin	Moxifloxacin
Lomefloxacin	Gemifloxacin
Ofloxacin	
Levofloxacin	
Rufloxacin	

a Most potent *vs* Pseudomonas.
b More potent *vs* Pneumococcus and anaerobes than earlier compounds.
c Most potent *vs* Pneumococcus and anaerobes.

7. Conclusions

This review has attempted to emphasise the importance of the quinolones in clinical medicine, and the advances that have already been accomplished in the introduction of new compounds that are truly innovative and will undoubtedly have new uses. The role of these newer compounds in clinical medicine is likely to grow substantially. Thus, the newer quinolones appear to have a very healthy future.

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