EDITORIAL

THE PLACE OF QUINOLONES IN MEDICINE TODAY

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Introduction

Antimicrobial chemotherapy began with the sulphonamides during the 1930s. During the intervening five decades, changes in the type of infection encountered as well as the emergence of bacterial resistance to older agents, have stimulated an ongoing search for new agents with greater potency and broad-spectrum activity.

The introduction of fluoroquinolones into clinical use is an important recent advance. The original prototype agent of this class is nalidixic acid, a chance by-product of chloroquine synthesis first described by Lescher et al in 1962[1]. The rapid emergence of resistant strains has limited the clinical usefulness of nalidixic acid and its immediate successors (oxolinic acid, pipimedic acid and cinoxacin) in the treatment of urinary tract infections. The newer fluoroquinolones have modified the original two-member ring of nalidixic acid (with a 7-piperazine and a 6-fluorine). These fluoroquinolones include: norfloxacin, pefloxacin, ciprofloxacin, enoxacin, ofloxacin, fleroxacin and lomefloxacin.

Mechanism of Action and Resistance

Quinolones inhibit replication of bacterial DNA by blocking activity of DNA gyrase (bacterial topoisomerase II). This enzyme catalyses the conversion of covalently closed circular DNA to a superhelical form by an ATP-dependent strand-breakage-resealing process[2].

Mechanisms of bacterial resistance include chromosomal mutations that either alter DNA gyrase or reduce drug accumulation in association with changes in bacterial outer membrane protein. Plasmid-mediated resistance has not yet been found in clinical isolates.

In-Vitro Activity

As a group, the fluoroquinolones are most active against aerobic gram-negative bacilli, including most *Enterobacteriaceae* and gram-negative cocci such as *N. gonorrhoea, N. meningitidis* and *Moraxella catarrhalis*. They are moderately active against *Pseudomonas aeruginosa* with ciprofloxacin being the most active quinolone.

The activity of quinolones against gram-positive aerobes varies. They have good activity against *staphylococci* – including *S. aureus* and coagulase-negative *staphylococci* resistant to methicillin and aminoglycosides – but many have only borderline activity against *streptococcus* and enterococcus [3]. None of the available agents would be considered an initial choice for *streptococcus pneumoniae, streptococcus pyogenes or enterococcus faecalis*.

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Ciprofloxacin, ofloxacin and others are active against *Chlamydia trachomatis, Mycoplasma and Legionella species*. Anaerobic cocci and bacilli, including *Bacteroides* and *Clostridium* are generally resistant. Ciprofloxacin and ofloxacin are active against mycobacteria (*M. tuberculosis, M. kansasii, M. fortuitum* and *M. xenopi*) but their activity against *M. avium-intracellulare* is only fair to poor.

Recently, pefloxacin, ofloxacin and ciprofloxacin were found to be active against *protozoa*, including *Plasmodium spp, Trypanosoma cruzi* and *Leishmania donovani*, but not against *Toxoplasma gondii*.

Recently developed fluoroquinolones (eg WIN 57273, sparfloxacin, OPC 17116, BMY 40062, PD 117558, PD 127391) show improved activity against gram-positive bacteria, *Chlamydia, Acinetobacter spp, Xanthomonas maltophilia* and *anaerobes*. A member of newer fluoroquinolones containing a cyclopropyl group, are active against *Mycobacterium leprae*. By contrast, the newer fluoroquinolones have similar or less activity against *P. aeruginosa* and *Enterobacteriaceae*.

Quinolones have bactericidal activity against most species of bacteria, with minimal bactericidal concentrations typically equal or two fold higher than the minimal inhibitory concentrations. Combination of quinolones with a ß-lactam antibiotic or an aminoglycoside tend to have no interaction, to produce additive effects or less commonly to be synergistic whereas antagonism is rare[4].

Pharmacokinetic Properties

Most fluoroquinolones have good oral bioavailability (>95%) and a marked post-antimicrobial suppressive effect on bacteria that are not killed, that limits the frequency with which they need to be administered. Binding to serum protein is 14 to 25%, thus facilitating penetration to body tissues and fluids. Their ability to penetrate CSF is low except for pefloxacin (40% of serum) and ofloxacin (90% of serum).

Elimination is both renal and non-renal for ciprofloxacin, enoxacin, fleroxacin and lomefloxacin, primarily renal for ofloxacin and primarily non-renal for pefloxacin. In elderly patients, peak serum concentrations may be 1.3-fold to 3.0-fold higher than in younger patients, reflecting increased oral absorption, reduced renal elimination or both.

Adverse Effects

The incidence of adverse reactions to quinolones have been low. Gastrointestinal symptoms are the most common, occurring in 2% to 10% of patients. Central nervous system reactions including headache, restlessness and insomnia, occur in 1% to 4% of patients. Allergic reactions have been infrequent (0.5% to 2%).

Routine use of quinolones in children or pregnant women is not recommended because of cartilage erosions in the weight-bearing joints of young animals given quinolones[5]. Small numbers of children have, however, generally tolerated ciprofloxacin, with uncommon joint symptoms reported[6].

Antacids containing magnesium or aluminium and ferrous

sulphate reduce the absorption of orally administered quinolones by the formation of non-absorbable chelates. The clearance of theophylline and caffeine is inhibited by enoxacin and to lesser extent by ciprofloxacin and pefloxacin.

Clinical Overview

Clinical studies have identified the specific areas of appropriate use of quinolones.

Urinary Tract Infections

For the treatment of uncomplicated urinary tract infections (UTI), norfloxacin, ciprofloxacin and ofloxacin have been highly effective (92% to 100%) and comparable to trimethoprim-sulphamethoxazole (TMP-SMX) in double-blind studies in which patients were treated for 3 to 14 days. Single dose therapy with quinolones for uncomplicated cystitis resulted in failure in one of every five women treated. Hence, a three day regimen is more effective than a single dose in the treatment of uncomplicated lower UTI in women.

For complicated UTIs, treatment with quinolones for 7 to 10 days, was similar or superior to treatment with TMP-SMX, ß-lactam antibiotics or other parenteral agents in their ability to eliminate bacteriuria.

In a small comparative study of patients with chronic prostatitis, treatment with norfloxacin for 4 to 6 weeks produced bacteriologic cures in 92% of patients as compared with 67% of those treated with TMP-SMX[7].

Sexually Transmitted Diseases

For gonococcal infection, single oral doses of a quinolone are highly effective (91%-100%) in curing urethritis and cervicitis including infection with strains of penicillinase-producing *N. gonorrhoea*.

Some of the newer fluoroquinolones may be suitable agents for the treatment of *Chlamydia trachomatis* infections and non-gonococcal urethritis. To-date, small studies with ofloxacin and fleroxacin appear to achieve cure rates of 85%-100% for chlamydial urethritis and cervicitis[8]. Single dose quinolone therapy has also proved effective for chancroid.

Gastrointestinal Infections

The fluoroquinolones represent the most active group against the bowel range of bacterial enteropathogens eg enterotoxigenic *E. coli* and *Shigella spp*. The quinolones have several advantages in the treatment of traveller's diarrhoea: high concentrations are achieved in the intestinal lumen following oral administration and resistance development is unusual. Quinolones are effective therapy for typhoid fever including multiple drug resistant strains and can eliminate the carrier state[9].

Respiratory Tract Infections

The newer quinolones achieve excellent concentrations in bronchial tissue, sputum and sinus secretions after oral administration. They should be a good alternative for the treatment of acute exacerbation of chronic bronchitis especially if sputum examination reveals gram-negative pathogens. In community-acquired pneumonia, drugs other than quinolones seem indicated because of the limited efficacy of the new quinolones in the treatment of severe pneumococcal infections and their poor activity against the anaerobic flora causing aspiration pneumonia. In contrast, new quinolones should be very suitable for treatment of nosocomial pulmonary infections due to gram-negative pathogens.

In patients with cystic fibrosis, oral ofloxacin and ciprofloxacin are as effective as parenteral antibiotics for pulmonary exacerbations due to *P. aeruginosa*. Quinolones should not be used chronically in cystic fibrosis and should be alternated with other antibiotics to avoid development of resistance. The use of quinolones for the treatment of pulmonary tuberculosis has been limited. In patients with infections due to multiple drug resistant *M. tuberculosis*, ofloxacin in combination regimens was only partially effective[10].

Osteomyelitis

Quinolones offer a significant advance in the treatment of acute and chronic ostcomyelitis, since they inhibit many of the multiple resistant gram-negative aerobic bacilli in complicated bone infections. Most of the reported studies have involved ciprofloxacin which achieved clinical cures in 60% to 80% of patients followed for 6 months to a year. The development of resistance in infections caused by *P. aeruginosa* and *S. aureus* was associated with failure. Osteomyelitis due to mixed aerobic-anaerobic infections especially in the presence of poor vascular supply should be treated with combination therapy with an anti-anaerobic agent eg clindamycin or metronidazole.

Skin and Soft-Tissue Infections

Oral ciprofloxacin and ofloxacin have been found to be comparable to intravenous cefotaxime in the treatment of serious skin and skin structure infections. Quinolones such as ciprofloxacin and ofloxacin are also active against methicillin-resistant strains of *S. aureus* (MRSA). Particular caution should be exercised in using these drugs in patients with such infections because of the increasing prevalence of resistance to ciprofloxacin in MRSA strains[11].

Other Uses

Parenteral quinolones may be useful as empiric treatment in febrile neutropenic patients. Studies with intravenous ciprofloxacin with aminoglycoside or ß-lactam antibiotics demonstrate equivalency to other antibiotic regimens for treating suspected or known gram-negative bacteraemia in febrile neutropenic patients.

Quinolones have been used prophylactically to prevent infections in afebrile patients with neutropenia. Oral norfloxacin, ciprofloxacin and ofloxacin were uniformly more effective than oral placebo, TMP-SMX or vancomycin-polymyxin B sulphate in preventing gram-negative bacteraemia.

Data on the treatment of bacterial meningitis with quinolones are limited. Intravenous pefloxacin and ciprofloxacin provide effective treatment for gram-negative bacillary meningitis including *P. aeruginosa* and *Acinetobacter*. Ciprofloxacin has been used successfully for the treatment of patients with invasive external otitis caused by *P. aeruginosa*.

A single dose 500mg of ciprofloxacin effectively eliminates nasopharyngeal carriage of *N. meningitidis*[12].

Conclusion

The usefulness and convenience of the quinolones for the treatment of a broad range of infections have already resulted in their extensive use. An alarming problem with the clinical use of the quinolones appears to be the rapid emergence of resistance, especially in the gram-positive organisms. There are potential clinical uses of quinolones with the improved antimicrobial activity of the newer fluoroquinolones against gram-positive bacteria and anaerobes, and novel applications in the treatment of atypical mycobacteria, intracellular pathogens and protozoa. Studies will continue to define additional roles and to redefine existing ones for new fluoroquinolones. As clinical experience with quinolones accumulate, our understanding of their optimal

use will evolve.

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