REVIEW ARTICLE

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Quinolones in Sexually Transmitted Diseases

State of the Art

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Abstract

Progress in the development of fluoroquinolones for the treatment of sexually transmitted diseases has been slow. New compounds have appeared with good *in vitro* activity against the gonococcus, *Chlamydia trachomatis* and the genital mycoplasmas. However, there have been increasing reports of clinically relevant resistance by the gonococcus, and chlamydial and mycoplasmal resistance *in vitro* has been described. Formally reported treatment studies have not been forthcoming, despite an emerging role for the newer fluoroquinolones in the ambulatory treatment of pelvic inflammatory disease.

A review of this subject in 1995 concluded that 'progress in the use of quinolones to treat sexually transmitted diseases (STDs) has been slow'.[1] The conclusion went on to affirm that, whilst there was widespread agreement that an important role existed for the use of these drugs in this area of infectious diseases, improvements were required that justified the need for further *in vitro* and *in vivo* research. What then has happened in the intervening years to progress this matter?

The 1998 CDC Guidelines for treatment of STDs continue to recommend a role for quinolones.[2] Ciprofloxacin is first-line therapy for gonorrhoea and chancroid and second-line for granuloma inguinale. Ofloxacin is also indicated for first-line gonococcal therapy and has a defined role for nongonococcal urethritis and cervicitis and the ambulatory management of pelvic inflammatory disease.

1. Syphilis

Clinically useful activity of fluoroquinolones against *Treponema pallidum* continues to be elusive. There are no encouraging reports in this area.

2. Gonorrhoea

The CDC Guidelines recommend the use of either ciprofloxacin (single 500mg oral dose) or ofloxacin (single 400mg oral dose). Table I lists the activity of some of the newer fluoroquinolones against *Neisseria gonorrhoeae*. Molecules that are unlikely to reach the marketplace have been excluded. The need for continuing research into the activity of quinolones against the gonococcus is highlighted by increasing reports of resistance worldwide. The National Committee for Clinical Laboratory Standards in the US defines *N. gonorrhoeae* as fluoroquinolone resistant if the MIC is ≥1.0 mg/L for ciprofloxacin or ≥2.0 mg/L for ofloxacin.[4] In addition, reduced susceptibility may be designated as MIC >0.06 mg/L for ciprofloxacin or >0.0125 mg/L for ofloxacin. Tapsall et al.[5] have charted the changing pattern of resistance in Sydney, Australia. The first strain with reduced sensitivity to ciprofloxacin was isolated in 1984 (MIC 0.25 mg/L). In 1990, strains with an MIC value >1.0 mg/L were

Table I. Activity of various fluoroquinolones against *Neisseria gonorrhoeae*[1,3]

Antibiotic	MIC (mg/L)
Clinafloxacin	0.002
Grepafloxacin (OPC 17116)	0.004
Sitafloxacin (DU6859a)	0.008
Ciprofloxacin	0.008
Levofloxacin	0.008
Gatifloxacin (AM1155)	0.015
Trovafloxacin (CP 99,219)	0.015
Ofloxacin	0.015
Moxifloxacin (Bay 12-8039)	0.03
Sparfloxacin	0.03

isolated and, by 1995, accounted for 3.1% of isolates. Some 2.6% of the total (160/604) had MIC values >16 mg/L. The percentage rose to 5% in 1996 and 12.4% in 1997. The percentage of high level resistant strains had fallen to 0.7% in 1997. In Ohio, USA, quinolone resistance rose from 2% in 1991 to 16% in 1994,[6] whilst in the Far East, Knapp reported a rise from 12% in the Philippines in 1994 to a staggering 72.6% in 1997.[7] The clinical significance of this decreased susceptibility was demonstrated in Singapore by Ng and colleagues.[8] A single oral dose of ciprofloxacin 500mg in patients with uncomplicated gonorrhoea resulted in a cure rate of 92% in patients infected with strains with reduced sensitivity (MIC 0.125 to 0.5 mg/L); the cure rate reduced to 40% in patients infected with strains having an MIC value >1.0 mg/L. Deguchi et al. reported the emergence of resistance during treatment of a patient with gonococcal urethritis.[9] The patient received oral ofloxacin 200mg 3 times daily for 5 days, and the pretreatment MICs of ciprofloxacin and ofloxacin against the isolate were 0.25 mg/L and 1.0 mg/L, respectively. Respective post-treatment MICs were 1.0 and 8.0 mg/L. Both the pre- and post-treatment isolates were found to have identical mutations in *gyrA* (Ser-91 to Phe) and *parC* (Ser-87 to Ile) genes. In addition, the post-treatment isolate showed reduced uptake of ofloxacin. The alteration of Ser-91 to Phe in GyrA of DNA gyrase was found by Tanaka et al. to be the commonest mutation in Japanese strains of fluoroquinolone-resistant gonorrhoea, accounting for 69% of strains.[10] Further, they reported that alterations in *parC* gene of topoisomerase IV only occurred in the presence of *gyrA* mutations. Ciprofloxacin-resistant strains showed a marked reduction in sensitivity to newer agents, including levofloxacin, sitafloxacin, gatifloxacin and sparfloxacin. Cross-resistance was also demonstrated by Carlyn and colleagues,[11] such that strains with reduced sensitivity to ciprofloxacin (MIC 0.25 mg/L) were 8-fold more resistant to moxifloxacin, sitafloxacin and clinafloxacin (MIC shift from <0.002 mg/L to 0.16 mg/L). Further studies by Deguchi et al. showed that *gyrA* and *parC* mutants were 4-fold more resistant to fluoroquinolones than strains with *gyrA* mutations only.[12]

Table II. Activity of various fluoroquinolones against *Chlamydia trachomatis*[1,17-24]

Antibiotic	MIC (mg/L)
HSR 903	0.03
Sitafloxacin (DU6859a)	0.06
Grepafloxacin (OPC 17116)	0.06
Moxifloxacin (Bay 12-8039)	0.06
Trovafloxacin (CP 99,219)	0.06
Sparfloxacin	0.06
Clinafloxacin	0.06
Gatifloxacin (AM1155)	0.12
SB 265805	0.12
Levofloxacin	0.5
Ofloxacin	0.5
Ciprofloxacin	1.0

There are few clinical trial reports with new quinolones in gonorrhoea. A single oral 200mg dose of sparfloxacin has been shown to be effective against acute gonococcal urethritis in men.[13] Grepafloxacin has been shown to be effective when compared with cefixime, both given as a single 400mg oral dose, for uncomplicated gonococcal infection in men and women.[14,15] In both studies, the single dose failed to eradicate reliably concurrent chlamydial infection in the grepafloxacin group. Trovafloxacin as a single 100mg oral dose was as effective as oral ofloxacin 400mg against uncomplicated gonococcal infection in men and women.[16]

3. Nongonococcal Infection

Table II lists the activity of newer agents against *Chlamydia trachomatis*. All show activity consistent with clinical efficacy. A disturbing report from Dessus-Babus et al.[25] describes the development of quinolone resistance in a laboratory-manipulated L2 strain. Strains were exposed either to ofloxacin or sparfloxacin. The MICs of these compounds against the resistant strains were 64 mg/L and 32 mg/L, respectively. Cross-resistance was found against the index drugs and also pefloxacin, sparfloxacin, ciprofloxacin and norfloxacin. The resistance was characterised as resulting from a point mutation in *gyrA* of Ser 83 to Ile. Salman and Ridgway (personal communication) have also produced laboratory-manipulated L2 isolates with ciprofloxacin and ofloxacin MIC values of 256 and 512 mg/L, respectively, and complete cross-resistance. These resistant strains have not yet been characterised. The clinical significance of these findings is unknown, but the ease by which the strains could be produced is of concern.

Although the precise role of genital mycoplasmas in nongonococcal infections remains uncertain, the activity of fluoroquinolones against them is of importance. Table III lists the activity of newer agents against *Mycoplasma hominis* and *Ureaplasma urealyticum*. In general, these compounds show greater activity against *M. hominis* than against *U. urealyticum*, with a 4- to 8-fold range within each species. There are few studies on the activity of fluoroquinolones against other genital mycoplasmas, so the recent report by Bébéar and colleagues is of particular interest.[26] Bébéar et al. described the activity of grepafloxacin, ofloxacin, sparfloxacin and moxi-

Table III. Activity of various fluoroquinolones against *Mycoplasma hominis* and *Ureaplasma urealyticum*[1,23]

Antibiotic	MIC range (mg/L)	
	M. hominis	*U. urealyticum*
Trovafloxacin (CP 99,219)	0.015-0.03	0.12-0.5
Grepafloxacin (OPC 17116)	0.015-0.06	0.12-1.0
Sitafloxacin (DU6859a)	0.06 (MIC_{90})	0.12 (MIC_{90})
Moxifloxacin (Bay 12-8039)	0.06 (MIC_{90})	0.12 (MIC_{90})
Sparfloxacin	0.008-0.015	0.06-0.5
Clinafloxacin	0.015-0.06	0.06-2.0
Ciprofloxacin	0.25-0.5	0.25-1.0
Ofloxacin	0.25-1.0	1.0-4.0

floxacin against *M. penetrans*, *M. fermentans* and *M. genitalium*, in addition to *M. hominis* and *U. urealyticum*.[26] Activity against the first 3 organisms was similar to the activity against *M. hominis* (table III). Further studies by this group have yielded *in vitro* resistant strains of *M. hominis*. Characterisation of these strains suggests that the primary target for sparfloxacin is DNA gyrase, whereas the target for ciprofloxacin, pefloxacin and ofloxacin is topoisomerase IV.[27]

Reports of clinical studies are few. Sparfloxacin (200mg day 1 followed by 100mg daily for 6 days) was as effective as standard doxycycline therapy for nongonococcal urethritis in men,[28] whilst grepafloxacin 400mg daily for 7 days and trovafloxacin 200mg daily for 5 days compared favourably with doxycycline in the treatment of endocervical chlamydial infection.[29,30] Other studies are in hand and the results awaited with interest.

4. Pelvic Inflammatory Disease

The use of fluoroquinolones for ambulatory treatment of pelvic inflammatory disease is attractive. The need to include metronidazole or clindamycin in the regimen[2] should be obviated by the anaerobic activity of the newer fluoroquinolones. As with other genital infections, formally published trials remain few. A study by Arredondo et al. compared oral ciprofloxacin plus clindamycin with parenteral single dose ceftriaxone followed by doxycycline, both groups treated for 14 days.[31] The choice of ciprofloxacin was unfortunate, but ofloxacin was unavailable to the investigators. Cases were laparoscopically confirmed. The prevalence of *N. gonorrhoeae* and *C. trachomatis* was low (2% and 11%, respectively). A 97% clinical cure was obtained with the ciprofloxacin regimen, compared with 95% for ceftriaxone and doxycycline. One of 2 patients with gonococcal infection treated with ciprofloxacin was positive at follow-up, but details of any confounding factors were not given. Trovafloxacin 200mg daily for 14 days compared favourably with ofloxacin 400mg twice daily plus clindamycin 450mg 4 times daily, both regimens given for 14 days.[32] Details of this study are not available, but 'eradication of baseline pathogens was found in 100% of the trovafloxacin group and 92% of the ofloxacin group, with clinical cure in 100 and 92%, respectively'. These are encouraging data, with an important potential application in the ambulatory management of pelvic inflammatory disease. Detailed published studies are awaited with interest.

5. Donovanosis

The treatment of 3 cases of Giemsa stain-confirmed penile donovanosis with ciprofloxacin 500mg twice daily has been reported.[33] A marked response to ciprofloxacin at 7 days was noted, with re-epithelialisation at 2 weeks. Duration of therapy was not stated.

6. Conclusion

Realistically, there has been little progress since the 1995 review.[1] Many new molecules have been produced, and extensive *in vitro* studies have demonstrated that activity of these compounds is of great interest to clinicians working in STDs. However, translation of these data into clinical trials has been very limited. Some of the compounds have now reached the market, or are to be launched imminently. Many have a licensed indication for STD therapy, but this is often based on limited peer-reviewed published data, and often limited in application. It is clear that until the economics of quinolone use for STD therapy are clarified, progress towards the clinical use of newer agents will be limited.

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