REVIEW ARTICLE

Drugs 1999; 58 Suppl. 2: 96-98
0012-6667/99/0002-096/$01.50/0

The Quinolones and Renal Infection

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Abstract

The fluoroquinolones are excellent drugs for the treatment of most patients with renal infection. Ciprofloxacin has proved its value in good clinical trials for uncomplicated acute pyelonephritis and has been used widely for complicated urinary tract infections with presumed renal infection.

Nalidixic acid and the related non-fluorinated quinolones, oxolinic acid and cinoxacin, were effective therapeutic agents for complicated urinary tract infections (UTIs) during the 1960s and 1970s, and many patients with refractory infections were cured with these agents.[1] Unfortunately, resistance emerged rapidly and limited their long term effectiveness.[2]

Norfloxacin was introduced in 1983 in the US and became an alternative treatment regimen for patients with UTI, including patients with presumed or proven renal infection.[3] However, its limited and variable gastrointestinal absorption prevented it from becoming a widely accepted and satisfactory oral regimen for patients with acute pyelonephritis and no parenteral regimen was marketed.

The introduction of ciprofloxacin and its widespread use for UTIs during the past decade has had a major impact on the management of patients with acute and chronic renal infection.[4,5] Ciprofloxacin, and probably some of the recently introduced quinolones, have very significant advantages for the management of these infections which will be reviewed in greater detail.

1. Advantages of the Quinolones for Treatment of Renal Infection

1.1 Bacterial Spectrum

For the past decade ciprofloxacin has had a substantial and sustained effectiveness against most urinary tract pathogens, including almost all Gram-negative rods that cause both uncomplicated and complicated UTIs. As a result, it is an excellent empirical regimen for patients with presumed renal infection where it can be used in most situations with the expectation that 90% or more of potential pathogens will be susceptible.[6] Its bacterial spectrum for presumed renal infection is comparable with that of the carbapenems and includes not only the Enterobacteriaceae but also *Pseudomonas aeruginosa*. Of interest, none of the recently introduced fluoroquinolones appear to be more effective than ciprofloxacin *in vitro* for Enterobacteriaceae or *P. aeruginosa*. Of particular note, few Enterobacteriaceae have emerged resistant over a decade of widespread use of ciprofloxacin.[6,7] Unfortunately, within the hospital setting, *P. aeruginosa* have become resistant due to the emergence of resistance and nosocomial clonal spread. As a result, hospital-acquired UTIs with renal involvement are now occasionally due to ciprofloxacin-resistant *P. aeruginosa*. At present all the newer fluoroquinolones are also ineffective against most, if not all, ciprofloxacin-resistant aerobic Gram-negative rods, so their introduction has not altered the potential choices for the treatment of UTIs in these patients.

1.2 Pharmacokinetics

Many of the newer quinolones are potentially superior drugs for treating renal infection due to their efficacy, long half-life with once- or twice-daily administration, high volume of distribution and penetration into sites that are inflamed or purulent. Also, the quinolones diffuse well into cysts and may even achieve adequate concentrations in obstructed urinary tracts. Most of the quinolones are excreted unmetabolised, so that their antibacterial activity is present in high concentrations in urine. Particularly in complicated UTI with obstruction, cysts and injured and inadequately perfused renal tissue, the ability of the fluoroquinolones to achieve bactericidal concen-

trations wherever microbial invasion is occurring leads to their preferential selection.

Many of the fluoroquinolones, including ciprofloxacin, can also be administered both parenterally and orally. The excellent absorption of most of the newer fluoroquinolones enables the switch from parenteral to oral therapy to occur without change in dosage. This facilitates an early switch from parenteral to oral therapy, often within 1 to 2 days of initiation of therapy as long as the patient is taking oral medication.

The pharmacokinetics of the fluoroquinolones in patients with reduced renal function also make them excellent therapeutic agents for patients with renal infection who have impaired renal function. For most fluoroquinolones, little dosage alteration is necessary. Also, the lack of important irreversible dose-related adverse effects enables dosage selection without major concern about blood or tissue concentrations, in contrast to some therapeutic agents where accumulation and sometimes further renal injury can occur if renal impairment is not recognised and dosage modified.

1.3 Pharmacodynamics

The quinolones exhibit concentration-dependent bactericidal effectiveness. The higher the plasma concentration above the minimum inhibitory concentration (MIC), the faster the kill rate.[8] Most of the quinolones are rapidly bactericidal, particularly at concentrations of 10- to 100-fold above the MIC of the pathogen. Within renal tissue and in urine this occurs readily with most of the newer fluoroquinolones for most Enterobacteriaceae.

P. aeruginosa is the only common problematic organism. The MIC_{90} for this organism for ciprofloxacin varies from 0.5 to 2.0 mg/L. Most of the newer fluoroquinolones will not achieve a concentration even 4-fold above the MIC for *Pseudomonas* spp., particularly if the MIC_{90} is ≥2 mg/L. At present, ciprofloxacin remains the only fluoroquinolone which has a consistent MIC_{90} for *P. aeruginosa* of 1 or 2 mg/L, or less in patients who have not previously been treated with a quinolone or infected within institutions where ciprofloxacin resistance has spread widely.

1.4 Adverse Events

The fluoroquinolones have been used widely in patients with renal infection and have been very well tolerated. Serious complications are very rare with ciprofloxacin and presumably will be unlikely with the newer fluoroquinolones. As a result, rashes, nausea, vomiting, diarrhoea and mild central nervous system effects are usually the only adverse effects about which patients need to be informed. Unfortunately, all the quinolones are contraindicated during pregnancy and breast-feeding and during childhood and early adolescence. These contraindications restrict their use substantially in large numbers of patients who would otherwise benefit from their use for renal infections.

2. Clinical Trials in Patients with Renal Infection

Over 200 clinical trials have been reported in which the quinolones have been used in patients with UTIs. Unfortunately, this vast amount of potentially useful data is of very limited usefulness in defining the indications, optimal dosage or duration of treatment for patients with renal infection.

The diagnosis of renal infection in patients with a UTI is itself problematic. However, invasive pyelonephritis is a diagnosis that can be made with considerable specificity and has been a most useful clinical entry point from which trials can be carried out.

In patients with acute pyelonephritis, the fluoroquinolones have been used widely in clinical practice with satisfactory outcome and excellent cure rates. Patients mildly to moderately ill with acute pyelonephritis can usually be managed with oral therapy with the fluoroquinolones and hospital admission is avoided.[8,9] However, compliance is essential and patients need to be followed closely until they have demonstrated a clinical response. Severely ill patients can be given parenteral therapy and switched to an oral regimen once improvement is apparent.

Studies with fluoroquinolones have demonstrated cure rates in acute uncomplicated pyelonephritis of 90% or better. In a recent study, Talan et al.[10] treated 378 women in a multicentre study with presumed uncomplicated acute pyelonephritis. Of the 127 women treated with a 1-week course of ciprofloxacin who completed follow-up, all were bacteriologically cured at 4 to 11 days and 92.6% were cured at 22 to 45 days. They concluded, in this very well conducted study, that a 1-week oral regimen of ciprofloxacin is a satisfactory choice for women with presumed acute pyelonephritis who are not severely ill.

Patients with complicated renal infections have been studied much less well.[11] However, there is considerable consensus that the quinolones are excellent choices for the reasons identified in section 1. In particular, in patients with injured renal tissue, obstructed kidneys or renal abscesses, microbial killing in most instances occurs very well despite the underlying complication. In a study in which norfloxacin was prescribed continuously to suppress infection in patients with presumed chronic renal infections, it was much

more effective than placebo over a course of 6 months.[12]

3. Unresolved Issues

A number of unresolved issues remain with the use of quinolones in renal infection, and further study is required to clarify the optimal regimens for their use.

(i) Are any of the newest fluoroquinolones more effective and the drugs of choice for empirical treatment of renal infection, or does ciprofloxacin remain the preferred therapeutic choice because of its *in vitro* efficacy and its substantive track record of effectiveness? Almost certainly there will be considerable market pressures to use the newer quinolones. However, at present there are little data to indicate that the newer fluoroquinolones should be chosen over ciprofloxacin unless there are specific pathogens resistant to ciprofloxacin and susceptible to these newer agents. At present these situations would be relatively infrequent and presumably will occur in less than 5% of patients, even among those with complicated UTIs.

(ii) Are there any strategies to treat patients with *P. aeruginosa* with any regimen that will not be complicated by development of resistance? As cross-resistance appears to be almost universal between ciprofloxacin and the newer fluoroquinolones for this pathogen, it remains a priority that ciprofloxacin or any other agents be used with very considerable care in patients with *Pseudomonas* UTI. The emergence of resistance and the loss of this effective oral regimen is always a serious consequence for the individual. Also, many of these individuals are cared for within institutions in which cross-infection between patients occurs, and the spread of resistant *Pseudomonas* may lead to multiple patients and their urinary tracts becoming infected with this resistant organism. Strategies to prevent this are essential and should be part of the use of ciprofloxacin or any of the fluoroquinolones in patients with *Pseudomonas* UTI. Although there is limited evidence for this practice, I usually initiate therapy in patients with proven *Pseudomonas* UTI with a dual regimen of a β-lactam (ceftazidime or a carbapenem) or an aminoglycoside together with ciprofloxacin to avoid selection of resistant mutants.

(iii) The duration of therapy with the fluoroquinolones needs further study. Talan et al.[10] found that 1 week was effective in patients with acute uncomplicated pyelonephritis. Further evidence is necessary in patients with a variety of complicated infections.

(iv) Further well-defined studies are urgently needed in patients with complicated infection. We still do not know what regimens are optimal with regard to dosage, duration and, on occasion, even selection of the fluoroquinolones in this common but poorly investigated patient population. Patients need to be stratified, complications need to be quantified and carefully defined and outcomes need to be identified. Only if this is done in a critical fashion will we ultimately have the optimal regimens for using the fluoroquinolones in patients with complicated renal infections.

(v) Can the fluoroquinolones be used in patients in whom currently other agents are selected because of 'contraindication'? In particular, amongst adolescent females, these agents may be necessary as resistance emerges to other therapeutic choices.

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