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Use of Quinolones in Osteomyelitis and Infected Orthopaedic Prosthesis

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Abstract

The present review provides an updated critical analysis of the use of quinolones in osteomyelitis and orthopaedic prosthetic infections. Only papers published in peer-reviewed journals and related to the following areas were selected: experimental osteomyelitis, penetration of quinolones into human bone, and clinical use in comparative and noncomparative studies. Local drug carriers impregnated with quinolones allow high local antibiotic concentrations to be achieved in experimental systems. Considerable clinical experience has been gained mostly with ciprofloxacin and ofloxacin. Cumulated results in clinical trials show clinical success rates of more than 90% in osteomyelitis caused by Enterobacteriaceae. The combination of quinolones and rifampicin for the treatment of staphylococcal osteomyelitis as well as orthopaedic prosthetic infections appears very promising in clinical studies with a small number of patients. However, further comparative studies using quinolones as single agents or in combination (versus standard parenteral therapy) remain necessary in osteomyelitis due to *Staphylococcus aureus* or *Pseudomonas aeruginosa.* In particular, studies with the newer quinolones should be strongly encouraged in acute or chronic osteomyelitis and in more complicated situations such as diabetic osteomyelitis or foreign-body infection.

The use of quinolones for the treatment of osteomyelitis is now an established therapeutic approach. The continued interest in the use of fluoroquinolones for the treatment of osteomyelitis has resulted in extensive clinical experience with these drugs. Most of the clinical experience has been acquired with compounds available on the market such as ciprofloxacin and ofloxacin. Additional experience has been gained with experimental animal models using newer agents or combination therapies that deserve further testing in humans.

Quinolones have several advantages over other traditional compounds in the therapy of osteomyelitis or orthopaedic prosthetic device infections because: (i) after an initial course of intravenous therapy they can be administered orally with excellent bioavailability; (ii) they are relatively non-toxic; (iii) they penetrate bone at sufficient concentrations to inhibit most members of the family of Enterobacteriaceae, and a large percentage of *Pseudomonas* spp. and *Staphylococcus* spp. strains.

This is our fourth review on the use of quinolones for the treatment of osteomyelitis[1-3] and we shall attempt to summarise the major features of previous reviews as well as recent knowledge that has been gained since our last review in 1995. Other reviews have also been published on this same topic.[4-10]

1. Clinical Definitions

From a practical point of view, we shall distinguish 3 types of osteomyelitis in adults that will be described as separately as possible throughout this review.[11] These 3 types of osteomyelitis may be further classified as acute or chronic: the term 'acute' osteomyelitis is used clinically to signify a newly recognised bone infection; the relapse of a previously treated or untreated infection is considered to be a sign of chronic disease. Clinical signs persisting for more than 10 days correlate roughly with the development of necrotic bone and chronic osteomyelitis. The clinical pattern may evolve over months or even years and is characterised by: low-grade inflammation; the presence of pus, micro-organisms, and sequestra; a compromised soft tissue envelope; and, occasionally, a fistula.

Haematogenous osteomyelitis follows bacteraemic spread, is seen mostly in children (which are not dealt with in this review) or elderly patients, and is characterised by local multiplication of bacteria within bone during septicaemia.

Osteomyelitis secondary to a contiguous focus of infection without vascular insufficiency follows trauma, perforation, or an orthopaedic procedure. It implies a first infection that, by continuity, gains access to bone. By definition, it can occur at any age and can involve any bone. In this group, it is useful to distinguish patients with a foreign-body implant because of the associated high susceptibility to infection and the usual necessity to remove the prosthesis to achieve cure.

Another useful group to distinguish clinically is patients with diabetic foot infection. This disease entity has several important contributing factors: diabetes and its metabolic consequences, poor blood supply, bone ischaemia and neuropathy, which probably all contribute to bone destruction.

2. Material and Methods

We followed the same approach as previously described[3] to collect relevant references related to quinolones and osteomyelitis.

2.1 Data Sources

English-language studies on the Medline databases were identified by use of the following keywords: quinolones, osteomyelitis, experimental models, clinical trials.

Manufacturers of quinolones sold in Europe and the USA were contacted and requested to supply published data. Positive responses were obtained from the manufacturers of ciprofloxacin, fleroxacin, levofloxacin, moxifloxacin, ofloxacin, pefloxacin and sparfloxacin.

2.2 Selection of Data

Studies were selected if they were published in peer-reviewed journals and dealt with the following areas:

- experimental osteomyelitis in animals
- penetration of quinolones into bone
- clinical use if they included at least 10 evaluable patients
- reviews of osteomyelitis and quinolones.

This led to the exclusion of a large number of case reports, abstracts of clinical studies presented at meetings and/or published in proceedings, or articles relating to the use of different quinolones in the same study without randomisation of patients. Studies that dealt solely with antibacterial penetration into bone were included, but several bone concentration values measured during monitoring or clinical studies were not included.

2.3 Evaluation of Clinical Trials

For each clinical study, the number of patients, number of centres involved, method of patient selection (consecutive or not), method of randomisation, comparator, length of therapy, route of administration, type of osteomyelitis, nature and duration of follow-up, as well as adverse effects, were analysed. Most of the data extracted have been shown in our previous review.[3]

For clinical response, success (cure) was defined as the resolution of all signs and symptoms of active disease at the end of therapy and after a post-treatment observation period.[12,13] Failure was defined as lack of success or improvement. Microbiological response was defined as presumptive eradication or failure. The latter category included suppression with relapse, failure, reinfection or superinfection.

For convenience, and based on the spectrum of susceptibility to quinolones, bacteria were grouped as follows: (1) Enterobacteriaceae: this included, among others, *Citrobacter, Enterobacter, Escherichia coli, Klebsiella, Morganella, Proteus, Providencia, Salmonella, Serratia*, and *Shigella* spp. (as defined in Cowan & Steel;[14]) (2) *Pseudomonas aeruginosa*; (3) *Staphylococcus aureus;* (4) *Staphylococcus*, coagulase-negative; (5) Other.

3. Results

3.1 Animal Studies

In view of the lack of well performed, large-scale, comparative clinical trials investigating the use of quinolones for osteomyelitis in humans, data obtained from animal studies remain extremely valuable. In particular, such studies allow statistical comparison of various groups of therapies. Several studies published from the 1980s onwards have shown excellent results with quinolones in experimental osteomyelitis and/or in the presence of a foreign body and the most interesting are reviewed below.

The rabbit model of *P. aeruginosa* chronic osteomyelitis has the relative advantage of assessing the rate of negative microbiological cultures after 3 to 4 weeks of therapy. In a rather classical paper, Norden and Shinners[15] reported excellent activity of ciprofloxacin but poor activity of tobramycin in this model.

The rat model of chronic osteomyelitis is a more difficult therapeutic model, as no cure is achievable and results are expressed as changes in the number of micro-organisms per gram of bone. Two good studies were performed in the rat model of chronic osteomyelitis due to methicillin-resistant *S. aureus* (duration of administration 21 to 30 days). In a study by Henry et al.,[16] vancomycin performed poorly, ciprofloxacin had moderate activity, and the best results were obtained with the addition of rifampicin to both regimens. Similarly, in a study by Dworkin et al.,[17] vancomycin and the quinolones ciprofloxacin or pefloxacin were ineffective when given alone, but their combination with rifampicin gave highly satisfactory results.

Bone infections in the presence of a foreign body are particularly difficult to cure. A model has been developed in our laboratory to test the effect of prophylaxis and treatment of infection in the vicinity of a foreign body. For this purpose, tissue cages are implanted subcutaneously into rats or guinea-pigs.[18] In this rat tissue cage model of foreign body infection due to methicillin-resistant *S. aureus*, Chuard et al.[19] showed moderate activity of vancomycin or fleroxacin, a significant enhancement of activity in response to the fleroxacin/rifampicin combination, and almost complete sterilisation of the tissue cages (including difficult-to-treat surface-adherent micro-organisms) with administration of a triple regimen of fleroxacin/vancomycin/rifampicin.

More recently, Crémieux et al.[20] have demonstrated the efficacy of sparfloxacin, in addition to its autoradiographic distribution pattern, in the rabbit model of *S. aureus* joint prosthesis infection. The highest radioactive levels of sparfloxacin were detected around the prosthesis but were quite low in nearly compact bone. The newer quinolone, sparfloxacin, performed better than pefloxacin and controls.

3.2 Concentration of Quinolones in Human Bone

Several well-conducted clinical studies have assessed the concentration achieved by quinolones in human bone. For more detailed information, see table II from our review paper published in 1995.[3] Most studies were performed in patients undergoing total hip replacement for osteoarthritis while, in some cases, patients treated for bone infection were studied.

Although these measurements have several methodological problems (including methods of extraction, blood contamination, and different kinetics in bone *vs* serum), they are useful because they provide an estimate of concentrations achievable in bone and allow comparison with the minimum inhibitory concentration (MIC) values against infecting micro-organisms. However, it should be noted that most of the studies were performed in healthy bone and few data are available regarding infected bone.[21]

Concentrations achieved in bone were proportional to the administered dose of quinolone. Peak bone concentrations were between 1 and 2 mg/kg for the most frequently used quinolones (ciprofloxacin and ofloxacin), while higher concentrations were obtained with pefloxacin.[22-27] These values were significantly higher than the MIC_{90} values against Enterobacteriaceae and within the range of sensitivity of staphylococci and a significant proportion of *Pseudomonas* species. In conclusion, when compared with concentrations achieved in bone with β-cephalosporins, quinolone concentrations in bone were extremely satisfactory.

3.3 Penetration of Quinolones into Bone using Experimental Drug-Carrier Systems

Several recent studies have shown interesting results concerning the potential utilisation of quinolones in local drug-carrier systems that allow significantly higher tissular antibiotic levels to be achieved. These studies show good bone concentrations of quinolones using cement beads in rabbits with biodegradable delivery systems containing ofloxacin or ciprofloxacin. Polylactides-coglycolides or biodegradable polymers using ciprofloxacin have also been used as carriers in rabbit models. Experimental drug carriers have been tested in the prophylaxis and therapy of experimental bone infection. Nicolau et al.[28] showed the usefulness of this prophylaxis in acute *S. aureus* osteomyelitis in rabbits using absorbable ofloxacin-impregnated beads. These rabbits also had lower infection rates compared with the control group. Nie et al.[29] demonstrated the use of a bioabsorbable polymer for the delivery of ofloxacin during experimental osteomyelitis treatment in rabbits, with good therapeutic efficacy. Ofloxacin polymer in the presence or absence of systemic ofloxacin improved the rates of sterilisation of *Pseudomonas* infection.

4. Clinical Treatment of Chronic Osteomyelitis with Quinolones

Most of the studies performed to date with the quinolones are open nonprospective (or sequential) and noncomparative.

Descriptions of patients selected for these studies suggest that most had chronic osteomyelitis that had failed to respond to a previous course of various other

antibacterials. Most of these studies have been described in detail in our previous review.[3]

Only the most widely used quinolones, ciprofloxacin and ofloxacin, have been used in a significantly large number of patients (n > 100 patients) in studies selected by our search strategy.[25,30-41]

4.1 Ofloxacin

Ofloxacin was used in 3 open studies that totalled 341 patients. The average dose was 200mg every 8 to12 hours and the duration of therapy was 3 to 6 weeks. Secondary effects were quite low and the cure rate was 89%. The microbial group with the highest failure rate was the *Pseudomonas* species. Among the above-mentioned patients, ofloxacin was used as antibiotic therapy in 301 patients with chronic post-traumatic osteitis, with a cure rate of 82%.[42]

4.2 Ciprofloxacin

Until recently, ciprofloxacin has been the most widely used quinolone for bacterial osteomyelitis. In our previous review,[3] we analysed the combined results from 236 patients obtained from 9 published trials. The usual dosage was 750mg twice daily for periods ranging from 6 weeks to several months. Tolerability was good: 28% of the patients were reported to have adverse effects, but most were minor (nausea, alteration in liver enzymes, or rash). The overall rates of clinical response after follow-up ranging from 2 to 21 months, indicated rates of 56% (cure), 11% (improvement), and 32% (failure).

Cumulative and comparative analysis of the bacteriological efficacy of ciprofloxacin in the above published studies showed a success rate of 92% for osteomyelitis due to Enterobacteriaceae. This high success rate should be tempered by considering the higher failure rate in patients with the following bacteria: *P. aeruginosa* (28% failure rate), *S. aureus* (25% failure rate), *Staphylococcus* coagulase-negative (11% failure rate), and *Streptococcus* spp. (22% failure rate).

More recently, Galanakis et al.[43] treated patients with chronic osteomyelitis caused by multi-resistant Gram-negative bacteria, with ciprofloxacin or ofloxacin for a mean duration of about 4 months and with a follow-up of between 2 to 5 years. They observed clinical success and bacterial eradication in 68 to 76% of patients. Most of the infections were due to *P. aeruginosa* and fluoroquinolone resistance developed in 13 to 18% of the isolates. Predictably, most of the cases where resistance developed were associated with the presence of a foreign body.

Most of the comparative studies using ciprofloxacin, although well performed, have been small and thus do not allow any statistical conclusions. Cumulative data from 4 such studies in which oral ciprofloxacin (usually 750mg every 12 hours) was compared with various parenteral antibacterials showed that, of the patients treated with ciprofloxacin (n = 94), 81% were cured, 2% improved, and 18% failed to respond.[44-49] In those patients treated with various parenteral therapies, the overall cure or improvement and failure rates were 85% and 15%, respectively (i.e. similar to quinolones). Adverse effects with parenteral antimicrobials were frequently severe (16%) and included phlebitis and leucopenia.

The difference between the 2 treatment groups did not reach statistical significance (cumulative p value = 0.75). However, to demonstrate equivalence ($p < 0.05$) of the 2 treatment arms in a well-designed clinical trial would require at least 392 patients in each group, assuming a cure rate of 80% (± 10%) with a study power of 0.8.

5. Quinolone Treatment of Osteomyelitis in Specific Situations

5.1 Diabetic Osteomyelitis

Although quinolones are quite widely used for the treatment of chronic osteomyelitis in diabetic patients, the available published data on the use of these agents include only small numbers of patients.[50] In the presence of severe vascular disease, failure is common regardless of the antibacterial regimen used. An open study by Peterson et al.[39] showed a successful outcome of 65%, after 1 year of follow-up, in 29 diabetic patients with osteomyelitis who were treated with ciprofloxacin. In contrast, Nix et al.[34] obtained a successful outcome in only 29% of 24 patients after 1 year of follow-up. More recently, Lipsky et al.,[51] reported a 71% success rate with ofloxacin in 21 patients with well-established diabetic osteomyelitis, a significant proportion of whom had undergone operations. Although not many well-performed clinical trials have been carried out in diabetic osteomyelitis, the latter trial results compare well with cure rates obtained in similar patients treated with ampicillin/sulbactam and imipenem/cilastatin.[52]

5.2 Combination Therapy for the Treatment of Infected Orthopaedic Implants

Until very recently, conservative therapy (i.e. minimal surgery and antibiotics) of prosthetic joint infection has led to major clinical failure. In a recent retrospective review of *S. aureus* prosthetic joint infection treated conservatively (without prosthesis removal),

Brandt et al.[53] analysed 33 *S. aureus* infections between 1980 and 1991. These patients were treated only by prosthesis retention followed by antibiotic therapy. An acceptable success rate was observed in only 12 patients. An unacceptable failure rate of 63% indicated to the authors that prosthesis removal is mandatory in these patients.

More recently, however, several very interesting studies using combined antimicrobial therapy, including quinolones, in prosthetic infections (without prosthesis removal) have been published.

On the basis of a considerable background knowledge gained from animal experiments (as described above[16,17,19]), Drancourt et al.[54] prospectively treated a cohort of 47 evaluable patients with *Staphylococcus*-infected orthopaedic implants with oral rifampicin (900 mg/day) plus ofloxacin (600 mg/day). Patients with infected hip prostheses were treated for 6 months and the prosthesis was removed after 5 months of therapy only if it was deemed to be unstable. Infected knee prostheses or bone plates were treated for 9 months. All cases of infected knee prostheses were removed after 6 months. The overall success rate of this series was 76% (35 patients). Eight out of 12 failures were related to resistant bacteria, 23 out of 26 patients whose prostheses were removed, and 13 out of 31 whose prostheses were not removed, were cured. These data continue to indicate that only a minority of prosthetic infections can be cured by conservative therapy without prosthesis removal. However, this study also suggests that antibiotic therapy directed against *S. aureus* could assist the surgeon For example, after a specified treatment time with ciprofloxacin/rifampicin, the surgeon could proceed with one-step exchange arthroplasty.

In a recent study, Widmer et al.[55] and Zimmerli et al.[56] treated early staphylococcal orthopaedic device-related infections with oral ciprofloxacin in the presence or absence of rifampin in a double-blind, randomised trial. 33 patients with stable orthopaedic devices (hip and knee prostheses or internal fixation) underwent minimal surgery with the prostheses in place. After an initial two weeks of flucloxacillin or vancomycin (with rifampin or placebo), patients were treated for 3 to 6 months (6 months for knee) with ciprofloxacin (2×500mg per day orally) and rifampin (900mg per day orally) or placebo (instead of rifampin). In the presence of rifampin, a 100% success rate was observed in the 12 *S. aureus*-infected patients. In the group treated with ciprofloxacin and placebo, in the presence of *S. aureus*, there were 4 failures and, in the 4 cases of *S. epidermidis* disease, there was one failure. In the latter failure, the strain was identified as identical to the initial infecting micro-organism by typing and exhibited development of ciprofloxacin resistance.[57] In conclusion, early staphylococcal prosthetic infection treated with debridement surgery and a combination of quinolone-rifampin, may be curative.

Brouqui et al.[58] attempted to treat *P. aeruginosa*-infected prostheses with a quinolone-containing combination therapy. A combination of ciprofloxacin/ceftazidime was administered for 6 weeks followed by oral ciprofloxacin for a long period of time. This combination cured 9/9 patients with infected osteosynthetic material and 4/5 patients with a hip or knee prosthesis.

6. Discussion

Analysis of reports relating to the area of quinolones and osteomyelitis allows several interesting conclusions, which are summarised below:

1. Animal models have shown:
   - excellent penetration of quinolones into bone
   - excellent activity against experimentally induced osteomyelitis due to Gram-negative rods
   - good results in osteomyelitis or foreign body infection due to staphylococci even in the presence of a foreign body, when quinolones were combined with rifampicin, and excellent results even against surface-adherent methicillin-resistant *S. aureus* in the presence of a foreign body, when quinolones were combined with rifampicin and vancomycin.
2. Concentrations of quinolones achieved in human bone appear satisfactory, exceeding the MIC_{90} against Enterobacteriaceae and in the range of sensitivity against a significant proportion of methicillin-sensitive staphylococci and *P. aeruginosa*.
3. Local devices impregnated with quinolones appear to allow quite high therapeutic concentrations to be achieved in the immediate surrounding area.
4. Most of the clinical studies performed with quinolones in osteomyelitis have been open and non-comparative. Microbiological analysis of osteomyelitis cases treated with oral ciprofloxacin shows a success rate of 92% for Enterobacteriaceae. Therefore, quinolones can be considered an optimal therapy for osteomyelitis due to these bacteria and no further clinical trials appear to be necessary.
5. However, in a cumulative analysis, infections due to *Pseudomonas* spp. and *S. aureus* were associated with a 4-fold increase in the failure rate (odds ratio 3.85; 95% confidence interval 1.97 to 7.50; $p < 0.001$) compared with the failure rate in osteomyelitis due to other pathogens. Therefore, for osteomyelitis due to *S. aureus* or *P. aeruginosa* and, in particular, in the presence of a foreign body, additional well-performed studies comparing quinolones (alone or in combina-

tion therapy) with more traditional parenteral therapy appear necessary. These studies should be performed in a sufficient number of patients to allow meaningful statistical conclusions to be drawn.
6. The combination of quinolones and rifampicin for the treatment of staphylococcal osteomyelitis, associated or not with the presence of a prosthesis, appears very promising and several pilot studies, both in animals and humans, have shown encouraging results. Further studies in this area should be strongly encouraged to confirm these very important findings.
7. Currently, in specific situations such as diabetic osteomyelitis, wider spectrum therapy (including better anti-anaerobe and staphylococcal/streptococcal coverage) appears to be a wise recommendation. It should be emphasised that very few clinical data are available with the newer quinolones that possess a wider spectrum and improved anti-Gram-positive and anti-anaerobe activity.
8. Studies with the newer quinolones should be strongly encouraged in osteomyelitis.
9. Overall, it should be emphasised that oral quinolones offer several advantages when compared with parenteral antibacterials. In particular, shorter hospital stays, lower costs, and avoidance of adverse effects associated with intravenously administered agents. One can conclude that oral quinolone therapy is an important advance in clinical medicine for the treatment of osteomyelitis which remains, nevertheless, a complicated and difficult-to-treat infection.

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