REVIEW ARTICLE

Drugs 1999; 58 Suppl. 2: 82-84
0012-6667/99/0002-0082/$01.50/0

Fluoroquinolone Treatment of Skin and Skin Structure Infections

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Abstract

When the causative pathogens are susceptible, the fluoroquinolones have been demonstrated to be highly efficacious in the treatment of both mild uncomplicated skin and skin structure infections as well as the more severe complicated infections involving these tissues, including infections of the feet of diabetic patients. These broad spectrum agents, particularly the newer fluoroquinolones with enhanced activity against Gram-positive bacteria, are ideal for treating the often polymicrobial complicated skin and skin structure infections. The wisdom of treating uncomplicated skin infections, which are primarily due to staphylococci and streptococci wherein more narrow spectrum β-lactam antibiotics would suffice, is questionable.

In the absence of a trauma-induced portal of entry, *Staphylococcus aureus*, *Streptococcus pyogenes*, and other streptococci are the predominant pathogens causing skin and skin structure infections in immunocompetent patients. Among patients who are immunosuppressed, or in whom major skin trauma provides a focus for initial infection, the pathogens involved include not only those noted previously but also Gram-negative bacilli. Anaerobic Gram-positive cocci and anaerobic Gram-negative bacilli are commonly encountered in infections initiated at the site of some wounds, e.g. decubitus ulcers, foot ulcers in diabetics, wounds associated with colorectal surgery, and bite wounds. As they have a broad spectrum of activity that includes many of the organisms causing skin infections, and because they are highly bioavailable after oral administration, fluoroquinolones are excellent candidates for treating skin infections and have been studied extensively in this capacity.

1. Antimicrobial Activity

The newer fluoroquinolones, those recently approved for clinical use or in later clinical trials, have enhanced antibacterial activity against *S. aureus* (methicillin-susceptible), *S. pyogenes*, and *S. agalactiae*. While retaining typical fluoroquinolone activity against Enterobacteriaceae, levofloxacin, sparfloxacin, trovafloxacin, clinafloxacin, gatifloxacin, and moxifloxacin typically have MIC_{90} values of ≤ 0.5 mg/L for these organisms (levofloxacin MIC_{90}s for *S. pyogenes* and *S. agalactiae* are 1.0 and 2.0 mg/L, respectively).[1] These compounds are similarly active against *Peptostreptococcus* spp. and trovafloxacin is uniquely potent against *Bacteroides* spp., *Prevotella* spp. and *Porphyromonas* spp.[2] Additionally, the fluoroquinolones as a class of antimicrobials, including these newer agents, achieve concentrations in skin and in blister fluid that are equivalent to those found in serum or plasma.[1]

1.1 Uncomplicated Skin Infections

Randomised trials have demonstrated that some fluoroquinolones are as effective as β-lactam antibiotics in the treatment of uncomplicated skin and skin structure infections, primarily cellulitis. Cure or improvement was noted in 105/114 (92%) patients treated with fleroxacin or 55/57 (96%) patients treated with amoxicillin-clavulanate, each administered by mouth for approximately 7 days.[3] Similarly, ofloxacin resulted in a favourable outcome in 72/73 (98%) patients compared with 63/65 (97%) patients treated with cephalexin.[4] Oral trovafloxacin 100 mg/day for 7 to 10 days resulted in cure or improvement in 286/329 (87%) patients compared with a cure rate of 84% in patients treated with either cefpodoxime 800 mg/day or flucloxacillin 2.0 g/day.[5] In 2 studies,

cure rates with levofloxacin 500mg daily were 96% (124/129 patients) and 98% (178/182 patients) compared with a cure rate of 94% for ciprofloxacin 1000 mg/day (116/124 and 182/193 patients, respectively).[6,7]

1.2 Complicated Skin Infections

In the treatment of complicated skin and skin structure infections, fluoroquinolones have performed favourably in randomised trials wherein they were compared with third generation cephalosporins, β-lactam-β-lactamase inhibitors and carbapenems (table I).[5,8-12] Patients enrolled in these trials had serious complex infections often involving surgical wounds or traumatic ulcers and were judged to require hospitalisation and intravenous therapy. Infections were caused primarily by Gram-positive cocci and/or Gram-negative bacilli and were often polymicrobial. As a result of their bioavailability, fluoroquinolone therapy was often administered orally whereas the comparator drug was given entirely, or initially, intravenously.

1.3 Diabetic Foot Infection

Limb-threatening foot infections in diabetics are commonly engrafted on ulcerations, called mal perforans, that result from repetitive unappreciated trauma to the neuropathic foot. Arterial insufficiency may also be a complicating factor. While *S. aureus* and *S. agalactiae* are prominent pathogens in all categories of these infections, Gram-negative bacilli, anaerobic Gram-positive cocci and anaerobic Gram-negative bacilli are often recovered from the more severe polymicrobial infections associated with ulcerations extending through skin and into subcutaneous tissues or bone.[13] Although anaerobes have been isolated commonly from more severely infected foot lesions, their role as pathogens and the requirement that anaerobes be treated specifically has been questioned, based on the favourable responses of patients to treatment with agents that have relatively limited potency against anaerobic Gram-negative bacilli.[14] However, this challenge is muted by the predominance of susceptible anaerobic Gram-positive cocci and the absence of specific data demonstrating successful therapy in cases from which more resistant anaerobic Gram-negative bacilli (relative to the therapy administered) have been recovered.

Because of their spectrum of activity and pharmacological properties, the newer fluoroquinolones are attractive antimicrobials with which to treat diabetic foot infections. Beam et al.[15] reported cure or improvement in 38/43 (88%) patients with foot infections treated with twice-daily ciprofloxacin 200mg intravenously followed by 500mg orally.

Peterson et al.[16] treated diabetic patients with foot infections with oral ciprofloxacin 1500 or 2000 mg/day. Patients with soft tissue infection were treated for 3 weeks and those with presumed osteomyelitis were treated for 3 months. Although the initial response using either ciprofloxacin dose was favourable in 39/47 (83%) patients, only 60% of patients were judged to have responded favourably at 1-year follow-up. Successful therapy at 1 year was significantly associated with closure of the initial ulcer at the end of therapy. In a randomised non-blinded trial in patients with moderately severe foot infections, Lipsky et al.[17] compared treatment with ofloxacin 400mg intravenously every 12 hours, given initially intravenously and later orally, with ampicillin sulbactam 1.5 to 3.0g intravenously every 6 hours, followed by oral amoxicillin-clavulanate 625mg every 8 hours. In patients with infection limited to soft tissue, favourable responses were achieved in 28/31 (90%) patients and 86% of patients treated with ofloxacin or an

Table I. Comparative studies of quinolone treatment of complicated skin and skin structure infections

Author (reference no.)	Drug, dose, route (mean days)	Cured/total (% evaluable)[a]
Gentry et al.[8]	Ciprofloxacin 1.5g PO	164/217 (76)
	Cefotaxime 6g IV	162/215 (75)
Fass et al.[9]	Ciprofloxacin 400mg IV/1-1.5g PO	46/58 (79)
	Ceftazidime 2-4g IV	28/39 (72)
Gentry et al.[10]	Ofloxacin 800mg PO (12)	42/43 (98)+
	Cefotaxime 6g IV (12)	49/50 (98)+
Parrish and Jungkind[11]	Fleroxacin 400mg IV (7)	74/90 (82)
	Ceftazidime 2-6g IV (8)	36/49 (73)
Pfizer[5]	Trovafloxacin 200mg IV/PO (10-14)	62/85 (73)+
	Piperacillin/tazobactam 13.5g IV/cefpodoxime 800mg PO (10-14)	81/105 (77)+
Johnson Pharmaceuticals[12]	Levofloxacin 500mg IV/PO (7-14)	139/145 (96)+
	Primaxin 2g IV/ciprofloxacin 1500mg PO (7-14)	145/156 (93)+

a + means cure plus improved/total evaluable.

IV = intravenously; **PO** = orally.

aminopenicillin-β-lactamase inhibitor, respectively. Favourable response rates were similar among patients with complicating osteomyelitis, 12/16 (74%) patients treated with ofloxacin and 3/4 (75%) patients receiving β-lactam therapy. The duration of therapy in both study groups averaged slightly over 20 days and was almost evenly divided between the intravenous and oral routes of administration. An open, non-comparative trial evaluated trovafloxacin in the treatment of diabetic foot infections (excluding patients with osteomyelitis). Trovafloxacin 200mg daily was initially administered intravenously and subsequently by mouth for a total of 10 to 14 days. A favourable response (cure or improvement) was reported in 179/206 (87%) patients 30 days after treatment.[5]

The treatment of pedal osteomyelitis in the diabetic patient has not been studied carefully. Studies suggest that aggressive surgery, which essentially excises all infected bone, allows a cure of osteomyelitis with 2 to 3 weeks of intensive parenteral therapy.[18] Some authors have suggested that pedal osteomyelitis can be cured with prolonged (3 months) oral therapy, although the diagnosis of osteomyelitis in the successfully treated cases has not been based on histopathological findings.[16,19] In either case, the potential role for fluoroquinolone therapy is great and warrants carefully focused trials.

2. Conclusion

Overall, fluoroquinolones appear highly efficacious in the treatment of mild, uncomplicated and more severe, complicated skin and skin structure infections, including those in the feet of diabetic patients. When the isolated pathogens are susceptible to the selected fluoroquinolone, therapy with the agent has a very high likelihood of being successful. The wisdom of using broad spectrum fluoroquinolones for the treatment of uncomplicated skin infections, including cellulitis in the unulcerated diabetic foot, should be questioned. These infections, which are almost exclusively caused by Gram-positive cocci, are more appropriately treated with narrow spectrum β-lactam antibiotics. However, complicated skin and skin structure infections that are often caused by Gram-negative bacilli and are frequently polymicrobial, can be effectively treated with a fluoroquinolone if the causative organisms are not resistant to the selected agent. The availability of trovafloxacin, with an expanded anaerobic spectrum of activity, significantly expands the range of soft tissue infections that might be considered for treatment with a fluoroquinolone. The bioavailability of these agents after oral administration permits early, if not initial, oral therapy for these infections.

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