Fluoroquinolones in Skin and Soft-Tissue Infections

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Abstract

Serious skin infections have usually been treated with one or more parenteral antibiotics. With the inception of the newer quinolones, this problem may be circumvented because this group of antibiotics is effective when taken orally. They penetrate the blister fluid inflammatory exudates. Their spectrum of activity encompasses the common Gram-negative organisms implicated in skin infections. They have varying degrees of activity against Gram-positive organisms including Staphylococcus and Streptococcus species. Their activity against anaerobes is poor. Ciprofloxacin has been used successfully in eradicating nasal colonization by methicillin resistant Staphylococcus aureus. Studies have shown that orally administered ciprofloxacin is as effective as intravenous cefotaxime in skin infections. Oral administration permit outpatient therapy and results in substantial cost reductions.

Key words: *Antibiotics, quinolones, skin, infection.*

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The treatment of skin infections can be confusing and complicated. The clinical picture is often not specific for a single causative organism. Gram stain from ulcers or abscesses may reveal multiple organisms. Some infections involving the skin can be treated with such simple regimens as astringent compresses, antiseptic washes or topical antibiotics, however, treatment of more serious infections may require hospitalization and administration of parenteral antibiotics.

The situation has become more complex in recent years due to additional factors. Methicillin reistant Staphylococcus aureus is emerging as a causative organism in some skin lesions, as are organisms such as Serratia marcescens, Providencia and Staphylococcus epidermidis.[1]

The newer fluoroquinolones have been shown to be highly effective when taken orally. The pharmacokinetics and tissue penetration of the fluoroquinolones have been studied in normal volunteers following oral and, when available, intravenous administration.[4] They are readily absorbed and are minimally affected by the presence of food in the gastrointestinal tract.[2,3] They have significant tissue penetration, and all of the fluoroquinolones readily penetrate the blister fluid inflammatory exudates. (See Table 1)

The spectrum of activity of the fluoroquinolones is very broad, including outstanding activity against

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Table 1. Penetration of fluoroquinolones into cutaneous tissues of humans.

Drug	Dose (mg)	Route	Drug concentration		
			Blister fluid (ug/ml)	Skin (ug/g)	Subcutaneous fat (ug/g)
Ciprofloxacin[5,6,7]	500	Oral	1.0 (67%)		
	750	Oral		4.0 (170%)	
Ofloxacin[8]	600	Oral	5.2 (47%)		
Enoxacin[9,10]	600	Oral	3.0 (81%)	2.2 (81%)	1.0 (39%)
Perfloxacin[11]	400	Oral	3.0 (59%)		

Table 2. Potency of fluoroquinolones against skin pathogens in vitro.*

Organism	MIC for 90% of Strains (ug/ml)			
	Ciprofloxacin	Ofloxacin	Perfloxacin	C1-934
Staphylococcus aureus	0.5	0.5	0.5	0.12
Streptococci Groups A, C and G	2.0	2.0	8.0	0.5
Enterococci	2.0	4.0	4.0	0.5
Escherichia coli	0.06	0.12	0.12	1.0
Enterobacter cloacae	0.12	0.5	0.5	0.5
Serratia species	0.25	2.0	1.0	2.0
Pseudomonas aeruginosa	0.25-1.0	2-8	32	8-16
Bacteriodes fragilis	8.0	8.0	32	8.16
Anaerobic Gram-positive cocci	2.0	4.0	8.0	0.5-1.0
Clostridium Sp.	8.0	8.0	64	4.0-8.0

*Adopted from Hooper and Wolfaom[4]

Enterobacteriaceae and other aerobic Gram-negative organisms. They have varying degrees of activity against Pseudomonas aeruginosa, Streptococcus pyogenes, Enterococci, Staphylococcus aureus and Staphylococcus epidermidis. Their activity against anaerobes is poor. (See Table 2)

Bacterial skin infections can be divided into primary and secondary. Primary pyogenic skin infections are most frequently caused by Staphylococcus aureus and streptococci which colonize and then infect the skin. Minimum inhibitory concentrations for 90% of strains are close to those levels achievable in the skin. These infections include impetigo, eryseplas, furuncles, carbuncles, and cellulitis.

Secondary invasion of wounds may be caused by borad spectrum of organisms. Surgical wound infections may be caused by Gram-negative bacilli. Decubitus ulcers and ischemic ulcers of the lower extremities are frequently colonized and secondarily infected with a mixture of anaerobic, Gram-positive, and Gram-negative bacteria.

Clinical experience with fluoroquinolones in treating skin infections is substantial. It can be broadly divided into the following groups:

1) Cellulitis, subcutaneous abscesses, and wound infections:

Ciprofloxacin was administered orally in a dose of 500-750 mg twice daily or 250 mg three times daily to 418 patients. Clinical cures were observed in 340 (81.3%) of the patients and clinical improvement in an additional 58 (13.9%). Failures were observed in only 4.8% (20) of the group.

Bacteriological data showed eradication of organisms in 70%-94% (mean 82%). Eradication rates for ciprofloxocin were lower for Gram-positive organisms than those observed for infections caused by Gram-negative aerobic bacteria. The minimum inhibitory concentrations for species Straphylococus and Pseudomonas sometimes increased during therapy but this was not associated with clinical failures. Therapy failed in one-quarter of anaerobic infections.

2) Infection in the diabetic foot

These infections are primarily caused by Staphylococcus aureus, but polymicrobial flora, including anaerobes may be responsible. Most therapeutic strategies use broad spectrum antibiotics usually in combination and may result in significant drug toxicities. Although fluoroquinolones may circumvent this problem, their use alone is not recommended due to inadequate anaerobic activity.[12]

3) Methicillin-presistant Staphylococcus aureus (MRSA) infection

An earlier study had assessed the efficacy of ciprofloxacin in eradicating MRSA colonization.[13]

Table 3. Open study assessing the efficacy of ciprofolxacin 750 mg orally bid in the treatment of methicillin-resistant Staphylococcus aureus colonization*

Courses of Therapy Administered	– 14
Eradication of colonization	– 11 (79%) patients
	– 47/56 (83.9%) sites
Recolonization (within 1 month)	– 4 patients
Treatment failures	– 3

*Adopted from Melligan et al[13]

Table 4. Uncontrolled clinical trials of ciprofloxacin* in none infections.

Number of evaluable paients	– 109
Mean duration of therapy	– 65 days
Resolution of clinical signs and symptoms	– 63 (60%)
Improvement of clinical signs and symptoms	– 28 (27%)
Number of organisms eradicated	– 133/165 (81%)

*Dosage schedule 500 or 750 mg orally twice daily.

Most of the 20 patients enrolled had colonization at multiple sites, including nares, perineum, and open skin lesions. Ciprofloxacin was given orally 750 mg twice daily for 7-28 days. Eight patients had possible adverse effects and were excluded. MRSA was eradicated from all sites in 79% of the remaining 11 evaluable patients. Generally a two- to three-week course of therapy was necessary before eradication occurred. Three failures were associated with development of bacterial resistance to ciprofloxacin. Colonization with susceptible organisms also recurred in 4 of 14 successfully treated patients within a month after cessation of therapy. These data are summarized in Table 3.

Other in-vitro studies have shown that oral ciprofloxacin may have the potential to become an effective agent for the therapy of MRSA infections.[14]

However, a later report[15] recognized the development of ciprofloxacin resistance in 10 of 21 new MRSA isolates during the clinical study. This group reported a six-month eradication in only three of 11 ciprofloxacin-plus-rifampin-treated patients. This study concluded that ciprofloxacin is usually not effective and may risk the development of ciprofloxacin resistance in MRSA in the hospital environment.

4) Miscellaneous

Ciprofloxacin has been used in traumatic Pseudomonas aeruginosa foot infections,[16] necrotizing otitis externa, and for bone infections. For the treatment of osteomyelitis, 25 uncontrolled trials have been conducted so far. One hundred nine evaluable courses of therapy have been administered. The usual dose of ciprofloxacin was 500-750 mg bid for a mean duration of 65 days. Clinical cures were seen in 63% and improvement in 28%. Thus, clinical response was seen in 83% of osteomyelitis patients who received the drug, and bacterial cure was achieved in 133/165 (81%).[17]

Several comparative studies have looked at the efficacy of the newer fluoroquinolones compared to the commonly prescribed antibiotics for skin infections. Four hundred evaluable patients were enrolled in 13 comparative studies of patients with infections of the skin and skin structures.[18] Ciprofloxacin administered orally in a dosage of 750 mg twice daily was as effective as cefotaxime given intravenously at 2g three times daily in the treatment of infected skin ulcers, abscesses, wound infections, cellulitis, and infected burns caused primarily by S. aureus or Gram-negative bacilli. Each agent afforded a cure of 78%, therapeutic failures occured in 2% of patients treated with ciprofloxacin and in 6% of those given cefotaxime. Bacteriologically, the response to both drugs was comparable, with 91% isolates being eradicated after ciprofloxacin therapy and 89% eradicated after cefotaxime. All 29 isolates of P. aeruginosa from the ciprofloxacin treated patients were eradicated, as compared with only 12 of the 21 strains from those treated with cefotaxime.

Another important aspect of prescribing antibiotics is the cost factor. In a prospective, double-blind, randomized multicenter trial using oral ciprofloxacin therapy and parenteral cefotaxime for the treatment of mild to moderately severe skin and skin structure infections, an average savings of $780 per course was observed with ciprofloxacin:

Ciprofloxacin – $8/day × 9.3 outpatient days = **$74.40.**

Cefotaxime – $96/day × 8.9 days (Drug Cost) + $200 × 8.9 days (Hospital stay for intravenous administration) = **854.40.**

Table 5. Thirteen controlled comparative trials of oral ciprofloxacin and IV cefotaxime in the treatment of skin and skin structure infections.

	Ciprofloxacin*	Cefotaxime†
Number of evaluable patients	196	204
Mean duration of therapy	9.1	8.9
Number of cures/total (percent)	146/196 (78)	145/204 (78)
Number of organisms Eradicated/total (percent)	295/324 (91)	314/353 (89)
Number of patients with adverse events possibly drug related/number enrolled	34/238 (14.3)	25/236 (11)

*The dose of ciprofloxacin was 750 mg by mouth twice dialy.
†The dose of cefotaxime was 2g intravenously twice daily.

In summary, fluorinated quinolones are effective in the treatment of skin and skin structure infections caused by a variety of bacteria including cephalothin-sensitive and resistant organisms.

Until more information is available, ciprofloxacin should probably not be recommended for eradicating nasal colonization by methicillin-resistant S. aureus. Orally administered, it is as effective as intravenously administered cefotaxime. Finally, oral administration of fluorinated quinolones may facilitate outpatient therapy and reduce the cost of drug administration when used in hospitalized patients.

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