Titolo rivista/libro: International journal of clinical pharmacology research

Titolo articolo/sezione: Intra-articular somastatin 14 reduces synovial thickness in rheumatoid arthritis : an ultrasonographic study

Autore/i: Coari G

ISSN: 0251-1649

DOI:

Anno: 1995

Volume: 15

Fascicolo: 1

Editore:

Pag. iniziale: 27

Pag. finale: 32

INT. J. CLIN. PHARM. RES. **XIII**(2) 75 – 79 (1993)

ORAL CIPROFLOXACIN FOR TREATMENT OF CHRONIC OSTEOMYELITIS

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Summary: *Seventeen adult patients with chronic osteomyelitis were treated with oral ciprofloxacin, 750 mg twice daily. Treatment ranged from 28 to 254 days. Efficacy was considered to be good, based upon clinical resolution observed in 13 patients (76%). Clinical and microbiological failure was observed in 3 patients (18%), and there was one case of reinfection. Tolerance was very satisfactory, since the adverse reactions were mild and transitory; these occurred in 7 patients (41%), being cutaneous rash in 4 patients and diarrhoea in 3 patients. No patient had to discontinue treatment. Thus, oral ciprofloxacin may be a useful option for the prolonged treatment of chronic osteomyelitis, provided that it is always associated with surgical debridement. Due to the probable development of ciprofloxacin resistance in the* S. aureus *multiresistant strain, already observed in two patients in the present investigation, it is suggested that for the treatment of such infections another drug with antistaphylococcal activity should be associated with the ciprofloxacin.*

Introduction

The treatment of chronic osteomyelitis is based on a surgical approach and on administration of antibiotics. Surgical debridement for removal of osseous sequestration performs an important role in the treatment, since bacteria remain viable in this material and impede the full action of antibiotics. The antimicrobial regimen necessary to eradicate the infectious agent would have dictated hospitalization, and if it were done by parenteral route for long periods would have resulted in high expenses (1, 2).

This study was made to evaluate the safety and efficacy of ciprofloxacin when administered orally to patients with chronic osteomyelitis. The characteristics of this antibiotic, a 4-quinolone structurally related to nalidixic acid, (3) are a wide spectrum of antibacterial activity, including remarkable effectiveness against Gram-negative aerobes and some Gram-positive bacteria such as *Staphylococcus aureus*. It presents also some interesting pharmacological and pharmacokinetic properties, namely a half-life of 3.5 to 4.0 h that permits its use twice a day, and the capacity of achieving a therapeutical concentration in the bones after oral administration (4, 5).

Patients and methods

Study design. This investigation was prospective and open. Patients 18 or more years of age who gave informed consent were eligible. Exclusion criteria were: infections caused by pathogens resistant to the study drug, pregnancy, history of

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previous hypersensitivity reactions to quinolones, abnormal renal function (creatinine clearance <70 ml/min or serum creatinine level >1.6 mg %) or infections that needed concomitant antibiotics with activity similar to the test drug. The study design was approved by the hospital ethical review committee.

Patients and treatment. Between October 1988 and September 1990, 17 patients entered the study. Hospitalized adult patients were enrolled if they presented histological diagnosis of chronic osteomyelitis in bone biopsy and an organism susceptible to ciprofloxacin was isolated. Oral ciprofloxacin was given in doses of 750 mg twice daily; if and when *Enterococcus faecalis* was isolated, ampicillin was added after ensuring that it had no activity similar to the test drug against the Gram-negative organism. Duration of treatment ranged from 28 to 254 days.

Bacteriological procedures. Bone biopsy was processed at the Microbiology Laboratory of the Hospital do Servidor Publico Estadual of Sao Paulo. The Kirby-Bauer method (6) was used to test antibiotic susceptibility. Organisms with an inhibition zone less that 12 mm in diameter were considered resistant to ciprofloxacin, whereas those with a zone larger than 18 mm were considered susceptible. Bone biopsy was collected at the end of treatment, when possible. The serum bactericidal titre was performed in 8 patients. Blood cultures were collected before treatment.

Laboratory evaluations. The following laboratory tests were performed: ESR, haemoglobin, haematocrit, total and differential leukocyte count in peripheral blood, platelet count, serum creatinine and BUN, blood glucose, potassium and sodium, and urinalysis. Blood samples were collected before, weekly during the first 4 weeks of treatment, monthly during and after the treatment for at least one year.

Evaluation of efficacy and safety. Response to therapy was evaluated on a clinical basis, and a bacteriological basis when possible. Patients had to present clinical signs of systemic and/or local infection with presence of purulence through the bone sinus tract, and had to meet the following criteria: bone biopsy culture rendering an organism susceptible to ciprofloxacin, histological diagnosis of chronic osteomyelitis, adequate bacteriological follow-up (when possible) after treatment, a minimal therapy time of 28 days, and a follow-up for at least 12 months. Patients who met all these criteria were classified as:- clinical resolution, improvement, or failure. Clinical resolution was defined as complete resolution of signs and symptoms of infection and complete healing by second intention of surgical wound at the end of treatment and for at least 12 months thereafter. Improvement was defined as substantial amelioration of signs and symptoms without complete clinical resolution. Failure was defined as the absence of any substantial improvement in signs and symptoms. Reinfection was defined as eradication of the infecting organism(s) followed by appearance of different organism(s) at the infected site within 1 month after the end of therapy. Superinfection was defined as the appearance of different organism(s) at the infected site during therapy, with new organism(s) considered to be the cause of an infectious process. Microbiological failure was defined as continued isolation of infecting organism(s) at the site of infection.

When clinical adverse reactions or abnormal laboratory tests were registered, the statements were qualified as:- probably, possibly or doubtfully drug-related. The reactions were classified as mild, moderate and severe.

Results

Seventeen patients were evaluated in the study. The mean interval from the diagnosis to the beginning of treatment with ciprofloxacin was 19 months (ranging from 15 days to 180 months). Clinical details are summarized in Table I. Average duration of treatment was 174 days; one patient (case 7) was treated for 28 days only (he presented patella osteomyelitis, whose treatment involved total resection). Eleven (65%) patients had been treated with other antibiotics before admission to the study. All patients were submitted to surgical debridement, but only one patient (case 8) refused to submit to a new procedure despite the continued isolation of the infecting organism during the treatment with ciprofloxacin.

Table I *Clinical details of patients (n = 17)*

Male/female	12/5
Mean age, years (range)	66 (40–94)
Mean interval from the diagnosis to the beginning of study, months (range)	19 (0, 5–180)
Mean duration of treatment, days (range)	174 (28–254)
Source of osteomyelitis	
– haematogenic	1 (case 7)
– diabetic foot	2 (cases 3 and 15)
– device for intravascular access	1 (case 1)
– cardiac surgery	1 (case 13)
– orthopaedic surgery	12
• total joint replacement	5 (cases 8, 10, 11, 12 and 16)
• internal fixation	5 (cases 2, 4, 5, 6 and 17)
• tumour resection + bone graft	2 (cases 9 and 14)

Bacteriological data. Twenty-two bacterial pathogens were isolated from different bones: 9 *S. aureus*, 2 *E. faecalis*, 3 *Enterobacter* spp., 2 *P. aeruginosa*, 2 *E. coli*, 2 *P. mirabilis*, 1 *P. rettgeri*, 1 *Klebsiella* spp. (Table II). Three patients (18%) presented polymicrobial osteomyelitis (case 9: *P. mirabilis* + *E. faecalis*; case 14: *E. coli* + *P. rettgeri* + *E. faecalis*; case 15: *S. aureus* + *P. aeruginosa* + *Klebsiella* spp.) and 14 patients (82%) presented monomicrobial osteomyelitis. Among the *S. aureus* isolated, four (45%) were multiresistant.

Table II *Bacterial pathogens isolated*

Organism	n %
Staphylococcus aureus	9 (41, 0)
Enterococcus faecalis	2 (9, 1)
Enterobacter spp.	3 (13, 6)
Pseudomonas aeruginosa	2 (9, 1)
Escherichia coli	2 (9, 1)
Proteus mirabilis	2 (9, 1)
Proteus rettgeri	1 (4, 5)
Klebsiella spp.	1 (4, 5)
Total	22 (100)

Clinical efficacy. Results are summarized in Table III. In three patients (18%) clinical and microbiological failure was observed. In two of these patients, it was probably caused by the emergence of resistance in the isolated organisms (cases 4 and 13: *S. aureus multiresistant*). In the third patient (case 8: *P. aeruginosa*) there was no developed resistance to ciprofloxacin, but there was continued isolation of the infecting organism, probably due to the patient's refusal to submit to a further surgical debridement. In one patient (case 9: *P. mirabilis* + *E. faecalis*) there was reinfection with a ciprofloxacin-resistant strain of organism (*P. aeruginosa*). In 13 patients (76%) there was resolution of osteomyelitis, as confirmed by the follow-up of at least 12 months.

Clinical adverse reactions. All patients were included in the safety and tolerance analysis (Table IV). Mild and transitory adverse reactions were observed in 7 patients (41%), cutaneous rash in 4 and diarrhoea in 3, with spontaneous remission. No patient had to discontinue the treatment.

Discussion

The present study has confirmed the safety and efficacy of orally administered ciprofloxacin for

Table III *Clinical outcome in evaluable patients*

Case no.	Infection sites	Organisms	SBT	CR	I	F
1	clavicle	*S. aureus*	1/4	X		
2	tibia	*S. aureus*	1/8	X		
3	phalange	*S. aureus*	1/16	X		
4	femur	*S. aureus*	NA			X
5	radius	*S. aureus*	1/16	X		
6	tibia	*Enterobacter* spp.	1/256	X		
7	patella	*S. aureus*	1/16	X		
8	femur	*P. aeruginosa*	NA			X
		P. mirabilis				
9	femur	+	NA			#X
		E. faecalis				
10	hip	*P. mirabilis*	NA	X		
11	hip	*S. aureus*	NA	X		
12	hip	*Enterobacter* spp.	1/4	X		
13	sternum	*S. aureus*	1/128			X
		P. rettgeri				
		+				
14	iliac	*E. coli*	NA	X		
		+				
		E. faecalis				
		S. aureus				
		+				
15	metatarsal	*P. aeruginosa*	NA	X		
		+				
		Klebsiella spp.				
16	femur	*Enterobacter* spp.	NA	X		
17	femur	*E. coli*	NA	X		
Total				13		4

CR (Clinical resolution); I (Improvement); F (Failure);
NA (not available); SBT (serum bactericidal titre).
* *Staphylococcus aureus multiresistant.*
# Eradication of organisms, but reinfection with *Pseudomonas aeruginosa* resistant to ciprofloxacin.

Table IV *Clinical adverse reactions*

Side-effect	Probably	Possibly	Doubtfully
Cutaneous rash	4	–	–
Diarrhoea	3	–	–
Total	7	–	–

chronic osteomyelitis treatment. The results of clinical efficacy that we obtained were similar to those of other investigators (7–9). We achieved clinical resolution in 76% (13 out of 17) of our patients, with a minimal period of follow-up of 12 months. Therapeutic failure was 18%, approximately similar to the results of other investigators (7, 8).

In agreement with recent reports in the literature (10, 11), we also observed the emergence of resistance of *S. aureus* in the course of treatment (cases 4 and 13 with *S. aureus multriresistant* isolated). In one patient (case 13) the serum bactericidal titre was 1/128 when determined at the end of the first week of medication, and 2 months after the end of treatment he was submitted to a new bone biopsy which yielded an *S. aureus* which was now resistant to ciprofloxacin. The other patient, who had a bone sinus tract infection persisting after the end of treatment, submitted to a new bone biopsy resulting in the isolation of a strain of *S. aureus* resistant to ciprofloxacin. It appears, in some cases of *S. aureus* aetiology, that therapy with ciprofloxacin will need combination with another antibiotic with anti-staphylococcal activity to prevent the development of resistance to ciprofloxacin.

Side-effects in this study were more frequent than those mentioned in the literature (7, 8), but no patient felt the need to discontinue treatment, as these side-effects were mild, transitory and showed spontaneous remission.

The oral treatment with ciprofloxacin proved to be useful for prolonged therapy of chronic osteomyelitis, always combined with surgical debridement. It presents a good tolerability, allowing ambulatorial use with confidence and satisfactory results; however it demands special attention for the possible emergence of resistance, particularly in *Staphylococcus aureus*.

Acknowledgement

This study was supported in part by Bayer, Brazil.

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