Diffusion of levofloxacin into bone and synovial tissues

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Objectives: The degree of penetration of an antibiotic into the infected site is an important determinant of therapeutic success. Levofloxacin is widely used in the treatment of serious infections. However, there are only few studies concerning its diffusion into bone tissue and none concerning its diffusion into synovial tissue. Our objective was to quantify levofloxacin bone and synovial tissue penetration and to compare our data with the breakpoint for susceptible organisms.

Patients and methods: In an open-label study, 12 subjects who were undergoing elective total hip replacement received a single, parenteral, 500 mg dose of levofloxacin. Plasma, cortical and cancellous bone, and synovial tissue samples were collected a mean of 1.2 h later and analysed by a validated HPLC method.

Results: The mean ± S.D. plasma concentration of levofloxacin at the time of bone removal was 7.5 ± 1.3 mg/L. The levofloxacin concentrations were 7.4 ± 2.2 mg/kg in cancellous bone tissue and 3.9 ± 1.2 mg/kg in cortical bone tissue. The levofloxacin concentration was 8.9 ± 2.1 mg/kg in synovial tissue. The mean ± S.D. ratios of levofloxacin concentration in bone and plasma (bone/plasma) were 1.0 ± 0.4 for cancellous bone tissue and 0.5 ± 0.1 for cortical bone tissue. The ratio of levofloxacin concentration in synovial tissue and plasma (synovial tissue/plasma) was 1.2 ± 0.4.

Conclusions: The concentrations of levofloxacin achieved in cancellous and cortical bone tissue and in synovial tissue are greater than the breakpoint for susceptible organisms, which is ≤2 mg/L.

Keywords: levofloxacin, diffusion, bone and synovial tissues, pharmacokinetics, bone and joint infections

Introduction

The degree of penetration of an antibiotic into the infection site is an important determinant of therapeutic success. This is particularly true during the treatment of osteoarticular infections, where fluoroquinolones are widely used, in part because these antimicrobial agents are known to penetrate well into most body tissues.1 However, although many studies have examined the diffusion of antibiotics into bone tissue, there are only few data concerning the diffusion of fluoroquinolones into bone tissue and none concerning their diffusion into synovial tissue.2

Levofloxacin, a recent fluoroquinolone, is characterized by a broad spectrum of activity against both Gram-positive and -negative pathogens, as well as Mycoplasma, Legionella, Chlamydia and Mycobacterium spp.3 The pharmacokinetic profile of levofloxacin has been widely described, but there are only few data concerning its penetration into bone tissue, and no study has been devoted to its penetration into synovial tissue.4

In the present study, we examined the cortical and cancellous bone tissue and the synovial tissue penetration of levofloxacin after a single, intravenous dose of 500 mg administered to volunteers undergoing total hip replacement surgery. The results were compared with the levofloxacin breakpoint for susceptible organisms.

Patients and methods

Study protocol

This was a single-dose, open-label, single-arm, non-comparative study. The protocol was approved by the local ethics committee and written informed consent was obtained from all the patients. Adult patients who were undergoing total hip replacement surgery were enrolled. Patients were excluded if they were allergic to fluoroquinolones, were receiving...
any other antimicrobial therapy or exhibited renal dysfunction, defined as creatinine clearance <40 mL/min or a serum creatinine concentration >200 µM.

Twelve patients (two men and ten women) with a mean ± S.D. age of 78 ± 11 years, height of 159 ± 4 cm, weight of 63 ± 12 kg and creatinine clearance of 1.1 ± 0.3 mL/min/kg completed the study.

Before surgery, patients received cefazolin 2 g intravenously as perioperative prophylaxis and then levofloxacin 500 mg was administered as a single 30 min intravenous infusion. Total hip replacement surgery involves resection of the femoral bone (which consists of cancellous and cortical bone tissue) and synovial tissue, followed by implantation of the prosthetic hip joint.

Blood samples were collected at the time of femoral bone and synovial tissue resection. All bone and synovial samples were taken from non-infected tissue. The exact time of sample removal was recorded and bone and synovial tissue samples were stored at –80°C until they were analysed.

**Drug assay**

Dosages of levofloxacin in plasma, and bone and synovial tissues were determined with HPLC, as described previously. The extraction mean recovery of levofloxacin from quality control samples was 90.8, 82.5, 89.9 and 92.1%, respectively, for plasma, and cortical bone, cancellous bone and synovial tissues. Intra-day and inter-day variabilities were <5% for plasma and <6.6% for bone tissues. The limits of detection were 0.05 mg/L and 0.20 mg/kg, respectively, for plasma and bone tissues, and the limits of quantification were 0.20 mg/L and 0.50 mg/kg, respectively, for plasma and bone tissues.

**Results**

Levofloxacin was well tolerated by all patients. The mean ± S.D. plasma concentration of levofloxacin was 7.5 ± 1.3 mg/L at 1.2 h after the infusion. The cancellous and cortical bone tissue concentrations were 7.4 ± 2.2 and 3.9 ± 1.2 mg/kg, respectively, at the time of bone removal, corresponding to a percentage penetration of levofloxacin of 100% and 50%, respectively. The mean ± S.D. levofloxacin concentration in synovial tissue was 8.9 ± 2.1 mg/kg, corresponding to a percentage penetration of 120% (Table 1).

**Discussion**

Levofloxacin penetrates well into most body tissues and fluids, with drug tissue concentrations generally greater than those observed in plasma. However, the important exception to the generally excellent fluid penetration of levofloxacin is cerebrospinal fluid, where concentrations of drug reach only 16% of simultaneous plasma concentrations, similar to other fluoroquinolones. Our study confirms this observation for osteoarticular tissues, showing percentage penetration into cancellous and cortical bone of 100% and 50%, respectively, and a percentage penetration into synovial tissue of 120%. Our results can be related to those reported in 2001 by von Baum et al., who reported a bone/plasma ratio of levofloxacin concentration of 0.77 for cancellous bone. Moreover, this is the first study to report a synovial tissue percentage penetration of levofloxacin of 120%. This is of importance, since synovial tissue is involved in the physiopathology of septic arthritis, and is therefore an important target for antimicrobial therapy.

Our study exhibited satisfying pharmacokinetic results, attaining cancellous and cortical bone, and synovial tissue levels above the levofloxacin MIC breakpoint for susceptible organisms, which is ≤2 mg/L. The findings of our study indicate that levofloxacin levels in cancellous and cortical bone tissue, and in synovial tissue after a single dose of 500 mg should be efficient against most of the susceptible microorganisms usually encountered in osteoarticular infections, such as Staphylococcus aureus, Staphylococcus epidermidis, Enterococcus spp. and Enterobacteriaceae.

However, our study is limited by the fact that it was performed using non-infected bone and synovial tissue samples; hence it would be hazardous to extrapolate the results to concentrations achieved in infected osteoarticular tissues, in which the disposition of antibiotics

Table 1. Levofloxacin concentrations in plasma, cancellous and cortical bone, and synovial tissues, and tissue/plasma ratios of levofloxacin concentration after a single intravenous infusion of 500 mg in patients undergoing elective total hip replacement surgery

<table>
<thead>
<tr>
<th>Subject</th>
<th>Time of sample removal (h)</th>
<th>LVX concentration in plasma (mg/L)</th>
<th>LVX concentration in tissue (mg/kg)</th>
<th>Tissue/plasma ratio of LVX concentration</th>
</tr>
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<tr>
<td></td>
<td></td>
<td>Cancellous</td>
<td>Cortical</td>
<td>Synovial</td>
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<tr>
<td>1</td>
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<td>5.5</td>
<td>10.6</td>
<td>4.1</td>
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<tr>
<td>2</td>
<td>1.5</td>
<td>6.4</td>
<td>3.9</td>
<td>2.8</td>
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<td>8.6</td>
<td>3.6</td>
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<td>1.0</td>
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<td>7.6</td>
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<td>0.7</td>
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<td>2.5</td>
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<tr>
<td>Mean</td>
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<td>7.4</td>
<td>3.9</td>
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<tr>
<td>S.D.</td>
<td></td>
<td>1.3</td>
<td>2.2</td>
<td>1.2</td>
</tr>
</tbody>
</table>

LVX, levofloxacin.
Levofloxacin diffusion into bone and synovial tissues

might be very different. Moreover, the patients included in the study are very old and had a moderate degree of renal impairment, and it is possible that this might not be a very representative population, from the physiopathological and pharmacokinetic points of view, of what could be considered an adult population.

In conclusion, our data indicate adequate penetration of levofloxacin into uninfected osteoarticular tissues in our study population, achieving concentrations in synovial tissue, and cancellous and cortical bone tissues far above the MIC breakpoint for susceptible pathogens generally encountered in bone and joint infections. These results suggest that levofloxacin should be effective in the treatment of most osteoarticular infections caused by susceptible microorganisms. However, given the availability of narrower spectrum and less expensive antimicrobial agents, levofloxacin may not be recommended as first-line therapy. Moreover, further clinical studies are required to prove the efficacy of levofloxacin in the treatment of osteoarticular infections.

Acknowledgements

Support was provided solely by institutional sources.

References