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Short Communication

Levofloxacin at the usual dosage to treat bone and joint infections: a cohort analysis

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ABSTRACT

Fluoroquinolones are recommended for the treatment of bone and joint infections (BJIs), and levofloxacin is commonly used in this setting. However, no pre-marketing clinical study has supported its use, especially its dosage, for treating BJIs. This study aimed to assess the benefit–risk ratio of levofloxacin administered orally at a standard dosage of 500 mg once daily (OD) in a cohort of patients with BJIs. The medical records of patients admitted to a large French teaching hospital for BJI over a 1-year period and managed by a multidisciplinary team were reviewed. Patient data were recorded on a standardised form and the outcome was assessed at the end of antibiotic treatment and after 1-year of follow-up. A total of 230 patients were included, of whom 79 were treated with an antibiotic regimen including levofloxacin (34%). Most BJIs (97%) were surgically treated by wound debridement and/or removal or replacement of the infected device. Adverse drug reactions to levofloxacin leading to treatment discontinuation occurred in three patients (4%). The antibiotic treatment duration was significantly longer in patients treated with levofloxacin compared with other antibiotic regimens (median, 13 weeks vs. 6 weeks). Post-treatment outcomes were considered favourable (total or partial recovery, including orthopaedics aftermath) in 89–93% of patients, with no significant difference between treatment groups. In conclusion, oral levofloxacin at 500 mg OD is a well-tolerated and efficacious antibiotic treatment for BJIs. Our approach of following-up all treated patients is a useful way to validate specific clinical practices.

1. Introduction

Bone and joint infections (BJIs) are considered 'difficult-to-treat' infections, especially if implanted devices are involved. The French [1] and American [2] Societies for Infectious Diseases, together with the main authors in this field [3,4], recommend using fluoroquinolones to treat such infections. The pharmacological characteristics of levofloxacin, especially bone diffusion, oral bioavailability and half-life (allowing the use of a single daily dose), suggest that it should clearly be used for treating BJIs. However, there is a lack of scientific evidence from clinical studies to support its use for this purpose. The recommendation and current clinical practices at Nantes University Hospital (Nantes, France) for the prescription of fluoroquinolones in a combination therapy regimen are to use oral levofloxacin at 500 mg once daily (OD) for bone infections caused by susceptible strains. The most likely combined antibiotic is rifampicin in the case of susceptible staphylococci. At the time of this study, the usual duration of treatment was 3 months for all bone infections, based on recommendations for prosthetic joint infections.

The objective of this study was to assess the safety of levofloxacin at a standard dosage for treating BJIs by describing treated patients and evaluating outcomes. A comparison with patients treated with an antibiotic regiment not containing levofloxacin was performed to ensure that the prognosis was at least equivalent in terms of risk–benefit ratio.

2. Patients and methods

2.1. Study design

A retrospective cohort study was performed at a French university hospital, which was approved by the Institutional Review Board of Nantes University Hospital.

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2.2. Study setting

A multidisciplinary team (surgeons, anaesthesiologists, microbiologists, hospital pharmacist, infectious diseases practitioner and epidemiologist) arrived at consensus decisions regarding diagnosis and treatment of BJIs. All decisions of this team are supported by current recommendations [1,2]. In particular, the diagnosis is systematically made by culture of tissue samples obtained during surgery and/or by puncture, before antibiotic therapy. Three to five samples were cultured for 14 days as recommended for the diagnosis of BJIs. According to our own recommendations, prescription of levofloxacin should be done in a combination therapy regimen, by the oral route, at 500 mg OD for infections caused by susceptible strains, preferably with rifampicin in the case of staphylococcal BJIs, over 3 months. The levofloxacin dosage should be increased in the case of body weight >100 kg and decreased in the case of renal clearance <30 mL/min [estimated by the Modification of Diet in Renal Disease (MDRD) formula]. According to the hospital process for BJIs, oral therapy was initiated only after the multidisciplinary team's decision, following surgery and bacteriological diagnosis. Prior to this, an intravenous antibiotic combination of β-lactams and glycopeptides was administered.

2.3. Data collection

Information was on patient demographics, diagnosis, bacteriology, and surgical and medical treatments were systematically and prospectively collected in a database during the multidisciplinary weekly meeting. All adult patients entered into the database during 1 year were enrolled in this study. Exclusion criteria included pregnant women, children, and patients suffering from meningitis associated with BJI (in cases of rachis involvement).

2.4. Patient outcomes

Outcomes were measured at the end of treatment and after 1 year of follow-up. Outcome definitions were as follows: (i) 'improvement' was defined as the cure of infection with functional recovery; (ii) 'partial improvement' was defined as the cure of infection with functional loss; (iii), 'not cured' was defined as the persistence or relapse of infection (clinical signs of infection and/or surgery with peri-operative signs of infection and/or tissue culture positive after antibiotic treatment); and (iv) death. Information was on antibiotic regimens and duration were collected and analysed as noticed by physicians during follow-up.

For levofloxacin-treated patients undergoing BJI-related surgery during the first year after BJI, a comparison of microbiology culture results was performed to detect resistance to fluoroquinolones. The only reported case of relapse was individually described with regard to clinical and bacteriological data.

2.5. Levofloxacin safety assessment

Adverse drug reactions in levofloxacin-treated patients were retrospectively and individually analysed because of their very low frequency. The severity of adverse effects was classified according to the Common Terminology Criteria for Adverse Events (CTCAE): (A) spontaneous regression; (B) regression after symptomatic treatment; (C) hospitalisation with no life threat; (D) hospitalisation with life-threatening risk; and (E) death. The drug causative assessment was done by pharmacovigilance on a routine basis (systematic notification of all suspected drug toxicities).

2.6. Statistical analysis

The database was retrospectively analysed. Kruskal–Wallis test was used to compare continuous data, and the χ^2 test or Fisher's exact test was used, as appropriate, to compare categorical data. For all comparisons, a P-value of <0.05 was considered to represent a statistically significant difference. All statistical analyses were performed using STATA v.12.1 software (Stata Corp., College Station, TX).

3. Results

3.1. Study population

A total of 230 BJI patients were included, of whom 79 were treated with an antibiotic regimen including levofloxacin (34%). The characteristics of infection and management are described in Table 1. Prosthetic joint infections and osteosynthesis device infections occurred in approximately one-half and one-quarter of the enrolled patients, respectively, and the lower limb was most commonly involved. Most BJIs (97%) were surgically treated by debridement and/or removal of the orthopaedic device (Table 1). There were no differences when treated with levofloxacin or not (Table 1) in terms of orthopaedic diagnosis and treatment. Regarding the frequency of micro-organisms, meticillin-susceptible *Staphylococcus aureus* (MSSA) was more prevalent in levofloxacin-treated patients; indeed, MSSA are usually susceptible to fluoroquinolones.

The levofloxacin prescription was systematically combined with at least one other drug. Among the 79 levofloxacin-treated cases, 5 were treated with a modified dosage of levofloxacin: 750 mg OD in 4 cases of obesity; and 250 mg OD in 1 case of chronic renal failure. The remaining 74 patients received 500 mg oral levofloxacin OD. These findings were consistent with the local recommendation for prescribing levofloxacin in BJIs.

3.2. Patient outcomes

The outcomes did not differ between the levofloxacin treatment group and the other antibiotics treatment group (Table 2), even if only MSSA BJIs were considered (Table 3). The longer antibiotic duration in the levofloxacin-treated group (median, 13 weeks vs. 6 weeks; $P = 0.01$) (Table 2) was consistent with the locally recommended 3-month antibiotic regimen for BJIs (regardless of the causative bacteria) and was marked in MSSA BJIs (mean, 11.1 weeks vs. 7.2 weeks; $P = 0.001$) (Table 3).

Five deaths occurred, including two from sepsis and three from other pathological conditions.

Among the levofloxacin-treated patients, one case of relapse was reported, involving a knee prosthesis infection due to *Streptococcus agalactiae* treated with a debridement–antibiotics–implant retention protocol 4 months after implantation. The infection relapsed after discontinuation of the combination clindamycin/levofloxacin regimen. The previously susceptible streptococcal strain demonstrated an intermediate level of susceptibility to levofloxacin and acquired resistance to clindamycin. Factors that may have played a role in this failure include infected implant retention and the use of clindamycin against a strain previously identified as being resistant to erythromycin.

3.3. Levofloxacin safety assessment

Potential adverse effects of levofloxacin were reported for three cases: insomnia (grade A); rash–hepatitis–pancreatitis–neutropenia–myalgia (grade C); and rash–hepatitis–acute renal failure (grade C). A definitive drug linkage to the two grade C adverse effects was not established, but levofloxacin treatment was stopped as a precaution in both cases because of the reaction severity.