Pharmacokinetic aspects of levofloxacin 500 mg once daily during sequential intravenous/oral therapy in patients with lower respiratory tract infections

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Levofloxacin is considered an effective antibiotic in the treatment of community-acquired lower respiratory tract infections (LRTIs). A study was carried out on 17 in-patients to assess the pharmacokinetics of a 500 mg once-daily switch intravenous (iv)/oral regimen of levofloxacin in the treatment of LRTI patients. Blood samples were collected under steady-state conditions at appropriate intervals. Levofloxacin plasma concentrations were analysed by means of HPLC and pharmacokinetic parameters were estimated using the WinNonlin pharmacokinetic software package. A lower clearance of levofloxacin (<2 mL/min/kg), conditioning both a longer elimination half-life (∼9 h) and a larger AUC₀–τ (∼80 mg/L·h), was observed for both routes in our patients than in healthy volunteers. These differences may be explained considering that levofloxacin is excreted mainly as unchanged drug by the renal route, and most of our patients (71%) were very elderly subjects whose renal function physiologically declines with age. The almost complete (≥99%) absolute oral bioavailability suggests that a comparable exposure to the iv regimen may be achieved after oral administration. The overall clinical success rate was 94.1%.

Keywords: levofloxacin, oral bioavailability, switch therapy, elderly

Introduction

Levofloxacin is characterized by rapid bactericidal activity and a broad antimicrobial spectrum, which make it an attractive agent for the treatment of community-acquired lower respiratory tract infections (LRTIs).¹⁻⁵ Unlike earlier fluoroquinolones, levofloxacin is active not only against many Gram-negative aerobic species (i.e. Moraxella catharralis, Haemophilus influenzae and Enterobacteriaceae),⁶ but also against the major Gram-positive aerobic microorganisms implicated in LRTIs, namely Streptococcus pneumoniae (including penicillin-resistant strains)⁷ and methicillin-susceptible Staphylococcus aureus (MSSA).¹,⁷ A population pharmacokinetic study in healthy volunteers showed that oral levofloxacin may achieve a higher level in the epithelial lining fluid than in plasma (1.16-fold), this exposure guaranteeing optimal efficacy against the extracellular pathogens involved in LRTIs.⁸ Moreover, thanks to its ability to penetrate the plasma membrane of eukaryotic cells, levofloxacin also exhibits a valid activity against intracellular pathogens responsible for atypical pneumonia, namely Mycoplasma pneumoniae, Legionella pneumophila and Chlamydia pneumoniae.⁹⁻¹¹

In a randomized prospective multicentre trial, File et al.¹² showed that intravenous (iv) and/or oral levofloxacin 500 mg once daily for 7–14 days was more effective than iv ceftriaxone 1–2 g once or twice daily and/or oral cefuroxime axetil
500 mg twice daily ± oral erythromycin 0.5–1 g four times a day in the treatment of 590 patients with community-acquired pneumonia (96% versus 90% clinical success). Likewise, a 500 mg once-daily dose of levofloxacin was shown to be effective in the treatment of both acute exacerbation of chronic bronchitis and community-acquired pneumonia sustained by macrolide-resistant S. pneumoniae.

On this basis, levofloxacin may be considered an effective alternative choice to the β-lactam plus macrolide combination in the empirical treatment of community-acquired LRTIs especially when an intracellular pathogen may be involved or when a high rate of penicillin- or macrolide-resistant S. pneumoniae or an allergy to β-lactams may be the concern.

Since levofloxacin may be administered either parenterally or orally, a sequential timely conversion from iv to oral therapy may be adopted for enabling both a cost-effective treatment of infections and an early hospital discharge.

The primary objective of our study was to assess the pharmacokinetic appropriateness and the interindividual variability of a standard switch iv/oral regimen of levofloxacin 500 mg once daily frequently used in routine clinical practice for the treatment of patients with LRTIs.

Patients and methods

Study entry criteria

This study was carried out on a cohort of 17 in-patients (10 male and seven female) empirically treated for LRTIs (community-acquired pneumonia or acute exacerbation of chronic bronchitis) at the Division of Pneumology, SM Misericordia Hospital, Udine, Italy. All the patients were treated with a standard levofloxacin regimen, irrespective of their body weight, sex and age, for a variable duration according to the clinical status: 500 mg iv once daily administered as a 1 h intermittent infusion for 4–9 days followed by 500 mg oral once daily until the end of the therapy (total duration of therapy being 9–17 days). Patients’ characteristics are depicted in Table 1. No patient presented with major renal or hepatic impairment.

The aetiological agents were assessed by cultures of sputum and, whenever isolated, their in vitro susceptibility to levofloxacin was tested. The MIC was determined according to NCCLS methods.

Study design

The pharmacokinetic evaluations of levofloxacin were carried out after having obtained an informed consent from each patient. Criteria for inclusion in the study were: age ≥ 18 years, serum creatinine < 1.5 mg/dL, antimicrobial monotherapy with levofloxacin.

The iv and oral pharmacokinetic evaluations were carried out under steady-state conditions, that is after at least 48 h of unmodified treatment by each route of administration. To avoid potential interactions, patients were fasted overnight before and for 3 h after levofloxacin morning administration and no antacid drugs were co-administered during the study period. Many of the patients were co-treated with other drugs, none of which had a known influence on levofloxacin pharmacokinetics. Blood samples were collected each time by direct venal puncture: before and 0, 0.25, 0.5, 1, 2, 4, 6, 8 and 11 h after the 1 h iv infusion; before and 0.5, 1, 1.5, 2, 4, 6, 8 and 12 h after the oral administration. All the samples were frozen at –80°C until assayed.

HPLC analysis

Levofloxacin plasma concentrations were analysed by means of an HPLC method validated in our laboratory, as previously described. This method was not stereospecific for levofloxacin in the presence of ofloxacin; however, since levofloxacin has been shown to be stereochemically stable and not to convert into ofloxacin in vivo, this did not interfere with the assay. Intra- and inter-assay coefficients of variation (CV) were always <10%. The lower limit of detection was 0.1 mg/L.

Pharmacokinetic evaluations

Individual patient’s concentration-versus-time data obtained were estimated by a two-compartment open model with first-order elimination using the WinNonlin pharmacokinetic software package (Pharsight Corporation, Mountain View, CA, USA). The pharmacokinetic parameters assessed after iv administration included: steady-state maximum plasma concentration (C<sub>max ss</sub>), volume of distribution at the steady-state (V<sub>s</sub>), distribution half-life (t<sub>1/2α</sub>), elimination half-life (t<sub>1/2β</sub>), total body clearance (CL) and area under the plasma concentration–time curve during the observational period (AUC<sub>0-∞</sub>). The pharmacokinetic parameters explored after

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**Table 1. Patient characteristics at baseline**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean ± S.D.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>70 ± 13</td>
</tr>
<tr>
<td>Gender</td>
<td>10 M/7 F</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>71 ± 15</td>
</tr>
<tr>
<td>SGOT (IU/L)</td>
<td>31 ± 20</td>
</tr>
<tr>
<td>SGPT (IU/L)</td>
<td>51 ± 35</td>
</tr>
<tr>
<td>SCr (mg/dL)</td>
<td>0.98 ± 0.26</td>
</tr>
<tr>
<td>CL&lt;sub&gt;CR&lt;/sub&gt; (mL/min/kg)</td>
<td>1.03 ± 0.40</td>
</tr>
</tbody>
</table>

CL<sub>CR</sub>, estimated creatinine clearance by means of the Cockcroft and Gault formula; SCr, serum creatinine (normal range = 0.6–1.4 mg/dL); SGOT, serum glutamic oxalacetic transaminase (normal range = 10–45 IU/L); SGPT, serum glutamic pyruvic transaminase (normal range = 10–40 IU/L).
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oral administration included: $C_{\text{max ss}}$, time to reach maximum plasma concentration ($T_{\text{max}}$), $V_{\text{ss}}$, absorption half-life ($t_{1/2k_a}$), $t_{1/2\alpha}$, $t_{1/2\beta}$, CL and AUC$_{0-\tau}$. The absolute oral bioavailability ($F_{os}$) was determined by means of the following formula: 

$$\frac{\text{AUC}_{\text{po}}(0-\tau)}{\text{AUC}_{\text{iv}}(0-\tau)} \times 100.$$

Since patients received standard levofloxacin dosages, to avoid bias due to interindividual differences in body weight, the dose-related pharmacokinetic parameters ($C_{\text{max ss}}$ and AUC$_{0-\tau}$) were also normalized with respect to levofloxacin dose per kg, and consequently to a dose of 1 mg/kg levofloxacin every 24 h.

**Assessment of clinical efficacy**

The clinical efficacy of the antimicrobial therapy was defined as follows. Cure was defined as complete resolution of clinically significant signs and symptoms of LRTI at the end of therapy; improvement was defined as partial resolution of clinically significant signs and symptoms of LRTI at the end of therapy; failure was defined as the need for a change in therapy during treatment because of the persistence or worsening of clinical symptoms of LRTI. Cure and improvement were considered as successful responses.

**Statistical analysis**

According to normal or non-normal distribution, the findings were expressed as mean ± standard deviation (S.D.) or median and range, respectively. Statistical analysis was carried out by t-test for paired data and/or Mann–Whitney Rank Sum Test as appropriate using SigmaStat (Jandel Scientific, GmbH, Erkrath, Germany). A statistically significant difference was defined as $P<0.05$.

**Results**

**Patients’ characteristics and microbiology**

Among the 17 patients included in the study, admission diagnosis was acute exacerbation of chronic bronchitis in 10 cases and pneumonia in seven cases. Despite appropriate microbial investigations, only five of these 17 LRTI patients (29%) had a microbiologically confirmed bacterial etiology. The infection was monomicrobial in three cases (Enterococcus spp., Pseudomonas aeruginosa, methicillin-susceptible S. aureus) and polymicrobial in two cases (Enterobacter aerogenes, H. influenzae and S. pneumoniae in one case; H. influenzae and Klebsiella pneumoniae in the other case).

All of these isolates were shown to be sensitive in vitro to levofloxacin (MIC < 1 mg/L).

**Pharmacokinetic analysis**

Mean (± standard deviation, S.D.) levofloxacin plasma concentration-versus-time profiles after both iv and oral administration are shown in Figure 1. Average levofloxacin $C_{\text{max ss}}$ was 10.71 mg/L immediately after the 1 h iv infusion and 7.93 mg/L at 1.23 h after oral administration, respectively. Levofloxacin pharmacokinetic parameters are summarized in Table 2.

Moderate linear relationships between estimated creatinine clearance (CL) and estimated creatinine clearance (CL$_{\text{CR}}$) by means of the Cockcroft and Gault formula.29

Dose-normalized data showed that for each mg/kg of levofloxacin, the mean dose-normalized $C_{\text{max ss}}$ reached was 1.46 and 1.22 mg/L, whereas the mean fractional AUC$_{0-\tau}$ guaranteed was 10.18 and 11.62 mg/L-h, for the iv and oral route, respectively.
Outcome of therapy

Clinical outcome. Median length of levofloxacin therapy was 5 and 6 days for iv and oral treatment, respectively. At the end of levofloxacin therapy, the overall clinical success rate was 94.1%, since 76.4% (13/17) of cases were cured, whereas 17.6% of cases (3/17) were improved. In the remaining 5.9% of cases (1/17), the therapy failed and, consequently led to a persistence of clinical symptoms of LRTI; a change in the antimicrobial chemotherapy (ceftazidime plus ciprofloxacin plus amikacin) was required.

Discussion

Our study compared the steady-state pharmacokinetic profile of a standard levofloxacin 500 mg once-daily regimen during a switch iv/oral therapy and assessed clinical outcome in LRTI patients.

Although our pharmacokinetic data were generally similar to those observed by other authors,25–27 a lower clearance, conditioning both a longer elimination half-life and a larger AUC, was observed after both administration routes in our patients than in healthy volunteers.25–27 These differences may be explained considering that levofloxacin is mainly excreted as unchanged drug by the kidney, and most of our patients were very elderly subjects (12/17 aged >71 years) whose renal function had physiologically declined with age, as definitely demonstrated by Cockcroft & Gault.28 Tani-gawara et al.29 in a premarketing population pharmacokinetic study found that the elderly exhibited a 32% reduction in levofloxacin clearance as consequence of a lower creatinine clearance. Likewise, Chien et al.30 showed that levofloxacin clearance after administration of a single 500 mg oral dose was significantly lower in elderly than in young volunteers (1.68 versus 2.49 mL/min/kg) mainly due to major differences in renal function. According to this hypothesis, a moderate linear relationship between levofloxacin clearance and creatinine clearance after both iv and oral administration was also found in our study.
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As a consequence of this reduced clearance, total body exposure to levofloxacin (AUC0–∞) was ~1.5-fold larger in our patients than in young healthy volunteers,26–27 but it was comparable to Chien’s findings in elderly volunteers.20

Normalized data showed that a wide interindividual variability for Cmax and AUC0–∞ persists irrespective of patient body weight (coefficient of variations between 25% and 41%). This is in agreement with other authors’ findings showing that interindividual variation in levofloxacin pharmacokinetics may largely be related to the estimated creatinine clearance either in patients with serious community-acquired infection31 or in ICU patients with early onset ventilator-associated pneumonia.22 In particular, in a population pharmacokinetic study, Preston et al.31 showed that the most important covariate influencing the clearance of levofloxacin in 272 patients with community-acquired infection was the estimated creatinine clearance.

Although iv levofloxacin should be considered the optimal route for initial empirical therapy in hospitalized patients with serious LRTIs, the oral route may represent both an effective and cost saving regimen in appropriately selected patients, namely from the commencement in mild to moderate LRTI outpatients or as a continuation therapy. An oral 500 mg once-daily levofloxacin regimen should be considered a valid therapeutic approach for LRTIs in malabsorption-free patients, since it provides an effective treatment at lower costs.19 However, other less expensive treatments based on β-lactams (i.e. cefuroxime) and macrolides (i.e. clarithromycin) may also represent a valid alternative for the sequential iv/oral therapy of LRTIs, especially when a risk factor for fluoroquinolone use exists (i.e. neurological disorders).

The almost complete (≥99%) absolute oral bioavailability and the mean oral Cmax was quite similar to that observed immediately after the 1 h iv infusion (7.93 versus 10.71 mg/L) suggest that a comparable exposure to the iv regimen may be achieved after oral administration of levofloxacin. The >100% average oral bioavailability (114%) suggests that a larger exposure for the oral than for the iv route might have occurred in some cases. Actually, since this was a within-patient study and the same dosage was administered for both routes, these results might have represented a hard-to-explain finding. However, it has to be considered that Chien et al.26 in a cross-over 500 mg iv versus oral single dose study assessing levofloxacin pharmacokinetics in 23 healthy volunteers, showed that the oral bioavailability of levofloxacin was of a similar extent (103 ± 10%). Moreover, in our patients the trend for a larger exposure after the oral route may be partially explained by the fact that a slight reduction in renal function was observed in some patients during the oral assessment. As a consequence, a mean 12% lower levofloxacin clearance (1.65 versus 1.87 mL/min/kg) leading to an ~1.15-fold longer average elimination half-life of levofloxacin (9.81 versus 8.77 h) was observed after oral compared with iv administration. In any case, no statistically significant difference between mean AUCs (both for absolute and normalized data) was observed after oral and iv administration of levofloxacin.

A successful clinical response was obtained in all but one patient (94%), in agreement with other authors’ findings showing that iv/oral therapy with levofloxacin 500 mg once daily was very effective (96% clinical success) in treating community-acquired pneumonia.12 Whereas the median duration of therapy was in line with many guidelines for LRTIs,15–17 in two cases it was decided to prolong treatment for 14 and 17 days, respectively, due to the severity of illness.

In conclusion, the switch iv/oral levofloxacin 500 mg once-daily therapy represents a valid approach in the treatment of LRTIs. The concentration-dependent pharmacodynamic bactericidal activity combined with the sufficiently long elimination half-life of levofloxacin justifies the once-a-day administration in patients with community-acquired LRTIs.

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References


