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Pharmacokinetics and Pharmacodynamics of Intravenous Levofloxacin in Patients with Early-Onset Ventilator-Associated Pneumonia

Federico Pea,[1] *Elena Di Qual*,[1] *Aldo Cusenza*,[2] *Loris Brollo*,[1] *Marco Baldassarre*[2] and *Mario Furlanut*[1]

1 Department of Experimental and Clinical Pathology and Medicine, Medical School, Institute of Clinical Pharmacology and Toxicology, University of Udine, Udine, Italy
2 First Department of Anaesthesia and Intensive Care Unit, S. M. Misericordia Hospital, Udine, Italy

Abstract

Objective: To investigate the pharmacokinetics of levofloxacin and the pharmacokinetic-pharmacodynamic appropriateness of its total body exposure in patients in the intensive care unit (ICU) treated for early-onset ventilator-associated pneumonia (VAP) with intravenous levofloxacin 500mg twice daily.

Design: Prospective non-blinded pharmacokinetic-pharmacodynamic study.

Participants: Ten critically ill adult patients with normal renal function.

Methods: Blood and urine samples were collected at appropriate times during a 12-hour administration interval at steady state. Levofloxacin concentrations were determined by high-performance liquid chromatography. Clinical and microbiological outcomes were assessed.

Results: Levofloxacin pharmacokinetics were only partially comparable with those obtained from literature data for healthy volunteers. Area under the concentration-time curve (AUC_τ) over the 12-hour dosage interval was about 30–40% lower than in healthy volunteers (33.90 vs 49.60 mg • h/L). The reduced exposure may be due to a greater clearance of levofloxacin (0.204 vs 0.145 L/h/kg [3.40 vs 2.42 mL/min/kg]), leading to a shorter elimination half-life (5.2 vs 7.6 hours). Cumulative urinary excretion during the 12-hour dosage interval confirmed the greater excretion of unchanged drug in these patients compared with healthy subjects (76% vs 68%). Coadministered drugs used to treat underlying diseases (dopamine, furosemide, mannitol) may at least partially account for this enhanced elimination in critically ill patients. Intravenous levofloxacin 500mg twice daily ensured a median C_{max}/MIC (maximum plasma concentration/minimum inhibitory concentration) ratio of 102 and a median 24-hour AUC/MIC ratio of 930 SIT^{-1} • h (inverse serum inhibitory titre integrated over time) against methicillin-sensitive *Staphylococcus aureus* and *Haemophilus influenzae*. The overall success rate of the assessable cases was 75% (6/8). Bacterial eradication was obtained

in all of the assessable cases (8/8), but a superinfection (*Acinetobacter anitratus,Pseudomonas aeruginosa*) occurred in three cases.
Conclusions: The findings support the suitability of intravenous levofloxacin 500mg twice daily in the treatment of early-onset VAP in ICU patients with normal renal function. Levofloxacin may represent a valid alternative to non-pseudomonal β-lactams or aminoglycosides in the empirical treatment of early-onset VAP. However, further larger studies are warranted to investigate its efficacy.

Ventilator-associated pneumonia (VAP) is the most frequent nosocomial infection occurring in critically ill patients admitted into the intensive care unit (ICU), since it may account for up to 40–50% of all ICU infections.[1] Several studies have shown that VAP may be associated with an increased mortality rate when an unsuitable antibacterial treatment has been chosen, either for timing or for inappropriate spectrum of antibacterial activity.[2,3] However, it has been clearly documented that two types of VAP with specific and different microbial patterns occur according to time of onset. Early-onset VAP occurs within 3 days of the initiation of mechanical ventilation, and late-onset VAP after more than 3 days.[4] Although late-onset VAP is usually associated with exogenous multiresistant bacterial strains acquired in the ICU setting (*Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *Stenotrophomonas maltophilia*), early-onset VAP is mainly due to endogenous non-resistant flora that, after oropharyngeal colonisation, has been aspirated into the respiratory tract by the patient.[1,5] Moreover, some risk factors have been shown to favour the appearance of resistant strains (methicillin-resistant *Staphylococcus aureus*) in VAP, among which prior administration of antibacterials and long hospitalisation are considered to be the most relevant.[5,6] On the other hand, the most frequently isolated bacteria in early-onset VAP without risk factors are *Haemophilus influenzae* and *Streptococcus pneumoniae*, whereas methicillin-sensitive *Staphylococcus aureus* (MSSA) was demonstrated to be frequently associated with early-onset VAP occurring in patients admitted to the ICU for traumatic and medical head injury.[1,7]

On these bases, according to the American Thoracic Society guidelines,[8] different strategies in the empirical treatment of VAP should be recommended. Early-onset VAP without risk factors may be treated with β-lactam/β-lactamase inhibitor combinations, second-generation cephalosporins, non-pseudomonal third-generation cephalosporins or fluoroquinolones, whereas any onset VAP with risk factors should be treated with a combination regimen involving a fluoroquinolone or an aminoglycoside plus an antibacterial agent providing antipseudomonal activity, such as third- or fourth-generation cephalosporins, antipseudomonal penicillins, carbapenems or aztreonam.

Levofloxacin is a fluoroquinolone antibacterial characterised by a broad spectrum of antibacterial activity against aerobic microorganisms, both Gram-negative and Gram-positive, which may cover most of the aetiological agents frequently responsible for early-onset VAP. In fact, levofloxacin retains much of the *in vitro* activity of ciprofloxacin and ofloxacin against aerobic Gram-negative microorganisms, but exhibits enhanced potency against both MSSA and *Streptococcus pneumoniae*, maintaining full antibacterial efficacy against the latter bacterium regardless of its penicillin sensitivity.[9] Therefore, levofloxacin may be considered a valid option in the treatment of early-onset VAP without risk factors.

However, critically ill patients often present some pathophysiological conditions that may frequently alter the pharmacokinetic behaviour of hydrophilic or moderately lipophilic antibacterical agents, such as levofloxacin, and therefore from a pharmacokinetic point of view they should be considered as a particular subpopulation.[10] Therefore, a study was planned to assess both the pharmacokinetics of levofloxacin and the pharmacokinetic-pharmacodynamic appropriateness of total body

exposure to this antimicrobial agent in ICU patients treated with high-dose levofloxacin for early-onset VAP.

Patients and Methods

Study Entry Criteria

This study was performed on a cohort of ten ICU patients (eight male and two female) admitted to the First Department of Anaesthesia and ICU, S. M. Misericordia Hospital, Udine, Italy. All the patients were treated with a standard intravenous high-dose levofloxacin regimen (500mg twice daily) irrespective of their bodyweight, sex and age because of early-onset VAP (≤3 days of mechanical ventilation). No patient presented major renal or hepatic impairment.

The Clinical Pulmonary Infection Score (CPIS) proposed by Pugin et al.[11] was calculated to determine the likelihood that each patient's clinical findings were related to VAP. This score for pneumonia ranges from 0–12 and includes six clinical variables (body temperature, leucocyte count, volume and character of tracheal secretions, arterial oxygenation, chest X-ray, Gram stain and culture of tracheal aspirate). Patients with pulmonary infection were distinguished on the basis of a CPIS ≥6.

The aetiological agents were assessed by cultures of tracheobronchial aspirates, and all the isolates were shown to be sensitive *in vitro* to levofloxacin. Minimum inhibitory concentrations (MICs) were quantified by means of a personal computer software-based system (Bio-Videobact; Biokit S.A., Barcelona, Spain) that enabled accurate reading of the results of antibacterial agar diffusion test plates.[12,13] The diameters of antibacterial growth-inhibition zones were quantified by digital imaging, and a correlation with antibacterial concentration every 1mm was established by regression analysis.

Study Design

The pharmacokinetic evaluations of levofloxacin were performed after having obtained from the nearest relatives of each patient informed consent to collect blood and urine samples. Criteria for inclusion in the pharmacokinetic study were: age >16 years, estimated creatinine clearance (CL_{CR}) by means of the Cockcroft and Gault formula[14] >50 mL/min, stable renal function (daily plasma creatinine fluctuation <0.3 mg/dL).

Levofloxacin disposition in both plasma and urine was assessed under steady-state conditions after at least 3 days of unmodified treatment.

Blood samples were collected through a venous catheter before and 0, 0.25, 0.5, 1, 2, 4, 6, 8 and 11 hours after the morning 1-hour intravenous infusion of levofloxacin 500mg. After centrifugation, plasma was stored at –80°C until assayed.

Urine samples were collected for the 0–2, 2–4, 4–8 and 8–12 hour intervals after the morning infusion of levofloxacin 500mg. The volume of each urine sample was measured, and a 20mL aliquot was removed and stored frozen (–80°C) until assayed.

Levofloxacin Analysis

Levofloxacin plasma and urine concentrations were analysed by means of a high-performance liquid chromatography (HPLC) method validated in our laboratory based on those of Wong et al.[15] and Mack[16] with some modifications, as previously described.[17] The analytical method chosen was not stereospecific, since levofloxacin has been shown to be stereochemically stable in body fluids without any metabolic inversion to D-ofloxacin.[18]

Briefly, 50µL of internal standard stock solution (tinidazole 60 mg/L), 250µL of phosphate buffer and 5mL of dichloromethane were added to 250µL of plasma sample for extraction. After centrifugation, the organic portion was separated, evaporated under nitrogen and then reconstituted with 150µL of mobile phase. An aliquot of 50µL was injected into a liquid chromatograph equipped with a UV detector (280nm) and eluted with a mobile phase of 82% potassium phosphate buffer plus 18% acetonitrile (pH 2.6) on a 5µm C_{18} precolumn linked to a 5µm C_{18} column at room temperature. Precision and accuracy were assessed by performing replicate analyses of quality control samples (0.2, 0.5, 1, 2, 5, 10 mg/L) against calibration standards, intra- and inter-

assay coefficients of variation (CV) always being less than 10%. The lower limit of quantification was 0.1 mg/L.

For urine extraction, 30μL of internal standard stock solution (tinidazole 1 mg/L), 250μL of phosphate buffer and 5mL of dichloromethane were added to a 100μL sample of urine. After centrifugation, the organic portion was separated, evaporated under nitrogen and then reconstituted with 500μL of mobile phase. An aliquot of 50μL was injected into the liquid chromatograph under the same conditions as described above for plasma samples. Precision and accuracy were assessed by performing replicate analyses of quality control samples (20, 30, 75, 250, 350, 500 mg/L) against calibration standards (25, 50, 100, 200, 300, 400 mg/L). Intra-day and inter-day CV were always less than 10%. The lower limit of quantification was 0.1 mg/L.

Pharmacokinetic Evaluation

Individual patient concentration-time data were analysed by a two-compartment open model with first-order elimination using the WinNonlin pharmacokinetic software package (Pharsight Corp., Mountain View, CA, USA). The pharmacokinetic parameters explored included maximum plasma concentration ($C_{max,ss}$), distribution rate constant (α), elimination rate constant (β), volume of distribution at steady state (V_{ss}), distribution half-life ($t_{1/2}\alpha$), elimination half-life ($t_{1/2}\beta$), total body clearance (CL) and area under the plasma concentration-time curve during the 12-hour observational period (AUC_τ). AUC_τ of levofloxacin was calculated by the linear trapezoidal method. CL and V_{ss} were calculated as dose/AUC_τ and (dose × $AUMC_\tau$)/AUC_τ^2, respectively (where $AUMC_\tau$ is the area under the first moment curve during the observational period).

The cumulative amount of levofloxacin excreted in urine during the 12-hour dosage interval was also calculated.

Assessment of Efficacy

The primary endpoint of the study was to assess the appropriateness of the total body exposure to levofloxacin by calculating the two most relevant pharmacodynamic parameters for the concentration-dependent bactericidal activity of fluoroquinolones, the C_{max}/MIC ratio and the area under the inhibitory curve (AUIC), i.e. 24-hour AUC/MIC.[19] According to previous studies,[20-22] C_{max}/MIC > 12.2 and AUIC > 125 SIT^{-1} • h (inverse serum inhibitory titre integrated over time) are considered valid thresholds for guaranteeing optimal drug exposure either to prevent the selection of resistant strains or to obtain clinical and microbiological cure.

Although this study enrolled a very limited number of patients, both clinical and microbiological outcome were also assessed. The clinical efficacy of the antimicrobial therapy was defined as follows. Cure was defined as complete or partial resolution of signs and symptoms of pneumonia at the end of therapy; failure was defined as the need for a change in therapy during treatment because of persistence or worsening of clinical symptoms of VAP.

Microbiological cure was assessed by repeating cultures of tracheobronchial aspirates at the end of the antimicrobial treatment and was defined as follows. Bacterial eradication was defined as elimination of the primary aetiological agent responsible for VAP; microbiological persistence was defined as failure to eradicate the primary aetiological agent responsible for VAP; superinfection was defined as the appearance of a new aetiological agent resistant to levofloxacin.

Statistical Analysis

The Kolmogorov-Smirnov test was performed to assess whether the data were normally or not normally distributed. According to normal or non-normal distribution, the findings were expressed as mean ± SD or median and range, respectively.

Results

Patient Characteristics and Microbiology

Patient characteristics are depicted in table I. Among the ten patients included in the study, admission diagnosis in the ICU was post-traumatic

Table I. Patient characteristics on the study day

Parameter	Value (mean ± SD)
Age (y)	49 ± 22
Sex	8 male, 2 female
Weight (kg)	81 ± 17
APACHE II score	15 ± 7
AST (IU/L)	50 ± 31
ALT (IU/L)	68 ± 36
Bilirubinaemia (mg/dL)	1.00 ± 0.81
CL_{CR} (mL/min/kg)	1.76 ± 0.49

ALT = alanine aminotransferase (SGPT); **APACHE** = Acute Physiology, Age, and Chronic Health Evaluation; **AST** = aspartate aminotransferase (SGOT); **CL_{CR}** = creatinine clearance estimated by the Cockcroft-Gault formula.

head injury in five cases, medical cerebrovascular accident in four cases, and cardiac and respiratory failure in one case (table II). Of these ten patients with early-onset VAP, nine had a microbiologically confirmed bacterial aetiology (table II). Infection was monomicrobial in eight cases, and two microorganisms were recovered in one case (MSSA and *Enterobacter aerogenes*). MSSA was the most frequent isolate, accounting for 60% of organisms.

Pharmacokinetic Analysis

The pharmacokinetic evaluation was performed after 4–6 days of unmodified treatment with standard intravenous levofloxacin 500mg twice daily.

The mean levofloxacin plasma concentration-time profile is shown in figure 1. Levofloxacin $C_{max,ss}$ was 8.19 ± 1.80 mg/L immediately after the 1-hour intravenous infusion of 500mg, whereas the trough concentration ($C_{min,ss}$) was 1.16 ± 0.64 mg/L before administration and 1.18 ± 0.63 mg/L at the end of the administration interval. Levofloxacin pharmacokinetic parameters are summarised in table III

Very good linear relationships between the estimated CL_{CR} and either CL (figure 2) or dose-normalised AUC_τ (figure 3) of levofloxacin were observed.

Dose-Normalised Results

Since the patients received a standard treatment (500mg twice daily) to avoid bias due to inter-individual differences in bodyweight, the dose-related pharmacokinetic parameters ($C_{max,ss}$ and AUC_τ) were normalised with respect to levofloxacin dose per kg, and consequently to a dosage of 1 mg/kg every 12 hours. For each mg/kg of levofloxacin given by the intravenous route every 12 hours, the mean dose-normalised $C_{max,ss}$ reached was 1.30 mg/L, and the mean fractional AUC_τ was 5.49 mg • h/L.

Urinary Excretion

During the 12-hour observational period, fluid balance was normal in all the patients with a mean diuresis of 1380mL. Mean cumulative urinary excretion of levofloxacin during the 12-hour dosage interval (figure 4) showed that about 80% of the administered dose was recovered in urine. Average percentage excretion of levofloxacin was about 34%, 25% and 16% during the 0–4, 4–8 and 8–12 hour intervals, respectively.

Outcome of Therapy

Levofloxacin Pharmacodynamics

In the fully assessable cases (seven of ten patients), both the thresholds for optimal bactericidal efficacy were exceeded in all the cases (table III). This standard intravenous levofloxacin regimen of 500mg twice daily led to a median C_{max}/MIC ratio of 102 (range 32–1116) and a median AUIC of 930 SIT^{-1} • h (range 310–11 248).

Clinical Outcome

Median length of levofloxacin therapy was 8 days. At the end of levofloxacin therapy, two out of ten patients were unassessable for efficacy, since one patient died on day 8 because of the underlying disease unrelated to the infection (cerebral haemorrhage) and one patient empirically treated with levofloxacin did not present a proven bacterial aetiology. The overall success rate of the assessable cases was 75% (6/8), whereas the failure rate was 25% (2/8).

Microbiological Outcome

Microbiological outcome was unassessable in two out of ten patients, since one patient was not re-

Table II. Admission diagnosis, aetiological agents of ventilator-associated pneumonia and pharmacodynamic determinants of efficacy for levofloxacin

Case no.	Underlying disease	Aetiological agent	AUC_{24} (mg • h/L)	C_{max}(mg/L)	MIC (mg/L)	AUIC (SIT^{-1} • h)	C_{max}/MIC	Clinical outcome	Microbiological outcome	Superinfecting agents
1	PHI	MSSA	50.10	7.91	0.04	1252	198	Cured	Eradicated	
2	PHI	MSSA	48.66	6.81	0.10	487	68	Cured	Eradicated	
3	PHI	MSSA	54.10	9.21	0.09	601	102	Cured	Eradicated	
4	CA	MSSA	83.74	6.73	0.09	930	75	Failure	Eradicated	*A. anitratus*
5	CA	MSSA	61.90	6.34	0.20	310	32	Failure	Eradicated	*P. aeruginosa*
6	CA	*H. influenzae*	76.32	11.09	0.01	7632	1 109	Cured	Eradicated	
7a	CA	MSSA	112.48	11.16	0.01	11 248	1 116	NA	Eradicated	*A. anitratus*
7b		*E. aerogenes*			<1[a]	>112	>11	NA	Eradicated	
8	PHI	*E. aerogenes*	48.02	6.48	<1[a]	>48	>6	Cured	Eradicated	
9	PHI	*P. aeruginosa*	60.00	7.63	<1[a]	>60	>7	Cured	NA	
10	RF	None	82.76	8.54	NA	NA	NA	NA	NA	

a Breakpoint.

AUC_{24} = steady-state area under the plasma concentration-time curve during a 24-hour period; **AUIC** = area under the inhibitory curve (= AUC_{24}/MIC); **C_{max}** = maximum plasma concentration; **CA** = cerebrovascular accident; **MIC** = minimum inhibitory concentration; **MSSA** = methicillin-sensitive *S. aureus*; **NA** = not applicable; **PHI** = post-trauma head injury; **RF** = respiratory failure; **SIT** = serum inhibitory titre.

evaluated at the end of therapy and one did not present a proven bacterial aetiology for VAP.

Bacterial eradication of the primary aetiological agent was obtained in all of the assessable cases (8/8). However, superinfection caused by microorganisms resistant *in vitro* to levofloxacin, namely *Acinetobacter anitratus* in two cases and *Pseudomonas aeruginosa* in one case, occurred in 38% of cases (3/8).

Discussion

Our study assessed the disposition and the efficacy of a high-dose (500mg twice daily) intravenous regimen of levofloxacin in ICU patients treated for early-onset VAP. When considering the study population, it should be pointed out that most (9/10) of the subjects were neurosurgical patients, and therefore these findings should be considered mainly applicable to this specific critically ill subpopulation. However, ICU patients frequently develop hyperdynamic physiological parameters irrespective of their underlying disease, and this may considerably increase their renal function, so that the same considerations might be representative for some other ICU populations.

As far as pharmacokinetic parameters are concerned, our findings are at least partially comparable to other authors' findings in healthy volunteers receiving the same regimen.[9,18,23,24] However, the mean steady-state total body exposure to levofloxacin during the 12-hour dosage interval (AUC_τ) was about 30–40% lower than in healthy volunteers (33.90 vs 49.60 mg • h/L).[9] This reduced exposure may be the consequence of a much greater mean levofloxacin clearance found in our patients than in healthy volunteers (0.204 vs 0.145 L/h/kg [3.40 vs 2.42 mL/min/kg]), leading to a shorter elimination half-life (5.2 vs 7.6 hours).[9] Cumulative urinary excretion during the 12-hour dosage interval confirms that a greater extent of unmetabolised levofloxacin was excreted by these patients than by healthy subjects (76% vs 68%).[9] Although these findings might partially have been related to different analytical and methodological procedures, they

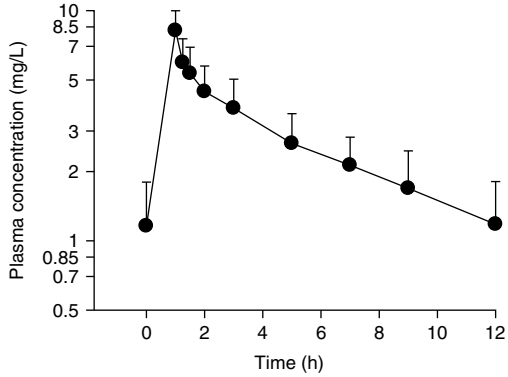

Fig. 1. Mean (± SD) steady-state levofloxacin plasma concentration versus time during multiple intravenous administration of 500mg twice daily in patients with ventilator-associated pneumonia (n = 10).

strongly suggest an enhanced levofloxacin elimination in our patients.

Considering that in these patients the renal clearance of levofloxacin was found to be greater than the creatinine clearance (figure 2), a surrogate marker for glomerular filtration, this suggests that active tubular secretion may occur in levofloxacin elimination. Although this relationship refers to an estimated and not to a directly measured creatinine clearance, it should be taken into account that Robert et al.[25] showed that the Cockcroft-Gault formula was an accurate predictor of glomerular filtration rate in mechanically ventilated critically ill patients. Therefore, these findings support the hypothesis that the increased levofloxacin clearance might have been related to an enhancement of both glomerular filtration and/or tubular secretion at the renal level.

Although it was not a major endpoint of our study to address this issue, it may be useful to suggest some factors that may at least partially account for this enhanced clearance in critically ill patients. Besides the well-known interindividual pharmacokinetic variability frequently observed in critically ill patients, coadministered drugs used to treat underlying diseases might have enhanced levofloxacin renal elimination in these conditions. In fact, some patients were cotreated with dopamine (one case) and furosemide (two cases) in order to increase cardiac output and to preserve renal function. Benmalek et al.[26] showed that low-dose dopamine administered to patients with post-traumatic head injury may enhance renal blood flow and, consequently, renal tubular secretion. Pea et al.[27] recently showed that drugs improving haemodynamics and/or diuresis (dopamine, dobutamine and furosemide) may enhance the renal clearance of a hydrophilic antimicrobial agent such as vancomycin in ICU patients. On this basis, considering that levofloxacin is almost exclusively cleared as unchanged drug by the kidney, dopamine and furosemide might have concurred in enhancing its renal tubular secretion.

Likewise, mannitol, which was coadministered to some other patients (four cases) because of increased intracranial pressure, could have potentially affected levofloxacin elimination. Mannitol is an osmotic diuretic which was shown to increase both glomerular filtration rate and renal blood flow.[28] Moreover, in animals, mannitol has been demonstrated to increase the renal clearance of digoxin, mainly by enhancing its tubular secretion through augmentation of renal blood flow.[29] Interestingly, in our study mannitol-treated patients demonstrated the highest values for levofloxacin clearance

Table III. Steady-state levofloxacin pharmacokinetic parameters during intravenous administration of 500mg twice daily in ten patients with ventilator-associated pneumonia

Parameter	Value (mean ± SD)
Dosage (mg/kg/12h)	6.37 ± 1.12
$C_{max,ss}$(mg/L)	8.19 ± 1.80
V_{ss} (L/kg)	1.22 ± 0.26
α (h^{-1})	4.15 ± 2.20
β (h^{-1})	0.14 ± 0.03
$t_{1/2\alpha}$ (h)	0.22 ± 0.13
$t_{1/2\beta}$ (h)	5.20 ± 1.33
CL (mL/min/kg)	3.40 ± 1.09
AUC_τ (mg • h/L)	33.90 ± 10.41
Dose-normalised $C_{max,ss}$(mg/L per 1 mg/kg/12h)	1.30 ± 0.22
Dose-normalised AUC_τ (mg • h/L per 1 mg/kg/12h)	5.49 ± 2.13
Cumulative urinary excretion (%) over the dosage interval	76.35 ± 9.24

AUC_τ = area under the plasma concentration-time curve during the 12-hour observational period; **CL** = total body clearance; **$C_{max,ss}$** = steady-state maximum plasma concentration; **$t_{1/2\alpha}$** = distribution half-life; **$t_{1/2\beta}$** = elimination half-life; **V_{ss}** = volume of distribution at steady state; α = distribution rate constant; β = elimination rate constant.

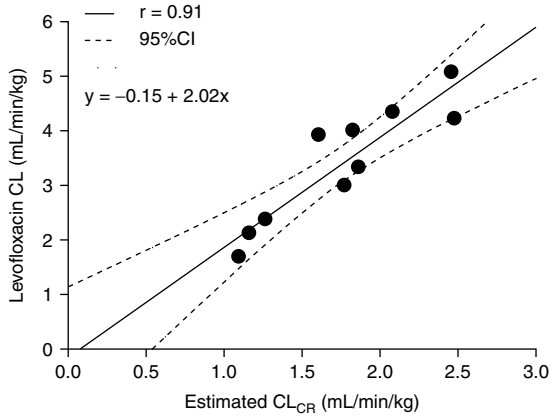

Fig. 2. Linear relationship between levofloxacin total body clearance (CL) and estimated creatinine clearance (CL_{CR}) in patients with ventilator-associated pneumonia (n = 10).

(2.08–4.34 mL/min/kg), and this seems to strengthen this hypothesis.

Whatever the mechanism responsible for the increased clearance of levofloxacin, the consequent shortening in $t_{1/2}\beta$ and reduction in AUC_τ of levofloxacin support the suitability of the 500mg twice daily regimen of levofloxacin to treat severe infection in ICU patients with normal renal function.

Accordingly, the pharmacodynamic analysis showed that both C_{max}/MIC and AUIC were consistently above the threshold for efficacy in all the assessable cases, suggesting that an optimal total body exposure to levofloxacin for preventing both clinical failure and the development of resistant strains is ensured by this regimen, notwithstanding that a superinfection sustained by intrinsically resistant bacteria occurred in three cases.

Another interesting observation is the relationship between the clearance of levofloxacin (figure 2), and consequently its dose-normalised AUC_τ (figure 3), and the estimated creatinine clearance for values ranging between 1 and 2.5 mL/min/kg (dose-normalised $AUC_\tau = 12.11 - 3.76\ CL_{CR}$; r = 0.87). Although this is derived from a limited number of patients, it may be considered an helpful tool for individualising the intravenous regimen of levofloxacin according to renal function in the ICU setting. This proposal is in agreement with other authors' findings concerning patients with serious community-acquired infection which suggested that interindividual variation in levofloxacin pharmacokinetics may be largely related to estimated creatinine clearance.[30] Therefore, once renal clearance has been estimated by means of the Cockcroft-Gault formula and the MIC of the isolate has been identified, it becomes possible to estimate the levofloxacin dose (mg/kg/12h) to be administered to achieve optimal drug exposure, i.e. AUIC > 125 $SIT^{-1} \bullet h$ (where $AUIC = 2 \times AUC_\tau/MIC$).

If an immediate value of MIC for the aetiological agent is unavailable, the MIC breakpoint could be considered for this estimation. However, it should not be neglected that our data support the concept previously suggested[31] that the pharmacodynamic breakpoint enabled by the standard levofloxacin 500mg twice daily dosage in this setting is lower than the *in vitro* breakpoint for susceptibility established by the National Committee on Clinical Laboratory Standards (NCCLS), namely 2 mg/L.[9] In fact, for optimal drug exposure against aerobic Gram-negative bacteria with an MIC of 2 mg/L, a C_{max} of at least 20 mg/L and a 24-hour AUC of at least 250 mg • h/L should be achieved, values at least 2-fold higher than actually achievable with such a regimen in most critically ill patients with normal renal function. Therefore, an MIC breakpoint of 1 mg/L for levofloxacin susceptibility in Gram-negative microorganisms might be more suitable.

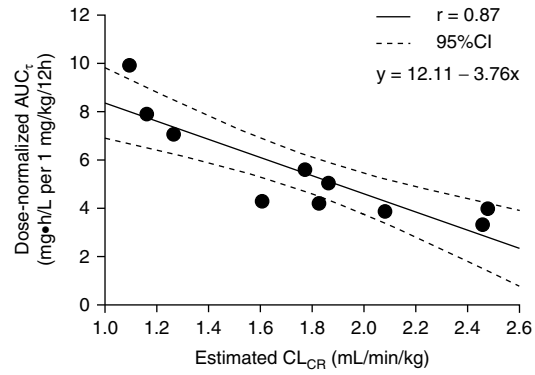

Fig. 3. Linear relationship between dose-normalised levofloxacin area under the concentration-time curve during the 12-hour observational period (AUC_τ) and estimated creatinine clearance (CL_{CR}) in patients with ventilator-associated pneumonia (n = 10).

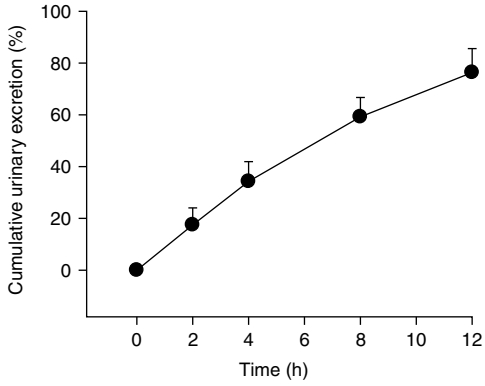

Fig. 4. Cumulative urinary excretion (mean ± SD) of levofloxacin at steady-state during a single dosage interval in patients with ventilator-associated pneumonia receiving 500mg intravenously twice daily (n = 10).

On the other hand, the NCCLS breakpoint of 2 mg/L for susceptibility to levofloxacin may be appropriate for aerobic Gram-positive microorganisms, namely MSSA and *Streptococcus pneumoniae*, considering that in recent studies an AUIC of 40 $SIT^{-1} \bullet h$ was documented to provide optimal exposure when these organisms were involved,[32-35] and that levofloxacin 24-hour AUC values of 80 mg • h/L may frequently be achieved with this twice-daily regimen.

Conclusions

Intravenous levofloxacin 500mg twice daily may be considered an effective regimen and may represent a valid alternative to non-pseudomonal β-lactams or to aminoglycosides in the empirical treatment of early-onset VAP. It may also be suitable for use in de-escalation therapy once an aetiological agent susceptible to levofloxacin has been identified. Furthermore, intravenous levofloxacin 500mg twice daily in combination with an antibacterial agent providing antipseudomonal activity might be an effective regimen in the treatment of late-onset VAP. Further larger studies are warranted to investigate its efficacy in these settings.

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Correspondence and offprints: Dr *Federico Pea*, Department of Experimental and Clinical Pathology and Medicine, Institute of Clinical Pharmacology and Toxicology, University of Udine, P. le S. M. Misericordia 3, 33100 Udine, Italy. E-mail: federico.pea@med.uniud.it