# Review of Clinical Pharmacokinetics of Levofloxacin with Special Emphasis in Burn Wound Patients

Ranjeet Prasad Dash, Rana Rais, and Nuggehally R. Srinivas

## 1 Introduction

Novel fluoroquinolones as a class have attained good prescription rate over the past two decades. The advantage of fluoroquinolones is that they provide options against gram-positive organisms and/or anaerobes while still maintaining impressive activity against gram-negative pathogens [1, 2]. Furthermore, it has been observed that newer fluoroquinolones provide distinctive pharmacokinetic profile with availability of higher drug concentrations in respiratory tract tissues and fluids relative to serum concentrations, following oral and intravenous administration [3, 4]. Amongst the novel fluoroquinolones, levofloxacin has gained significant importance in managing community-acquired pneumonia [5]. Levofloxacin (Fig. 1) offers broad-spectrum antibacterial activity especially against gram-negative organisms [5]. From the pharmacokinetic perspective, levofloxacin can be used both via oral and intravenous routes since it exhibits higher systemic and tissue concentrations after both oral and intravenous administration [5]. Levofloxacin is also a preferred drug for the management of burn-associated infections [6].

A major concern associated with the treatment in burn injury patients is the effect of pathological condition on the pharmacokinetic disposition of the drug being used in the treatment [5]. The pathological changes that occur in a burn injury patient have been suggested to have pharmacokinetic implications which may result in the alteration of either protein binding, volume of distribution, clearance or oral bioavailability [7]. The extent of impact on the pharmacokinetics of the drug is dependent on the type and degree of burn injury and the time that elapsed between burn injury and drug administration [7]. It should also be noted that burn/thermal injury would result in the enhanced intestinal permeability that will subsequently increase the bioavailability of large and hydrophilic molecules [8]. Because the levels of albumin and α1-acid glycoprotein decrease in burn injury patients, it may lead to increase in the free fraction of the drug in plasma [9]. The volume of distribution may change as a result of altered protein binding and/or enlarged extracellular volume [10]. The above mechanistic episodes with other related changes such as glomerular filtration rate, tubular secretion, hepatic blood flow and drug-metabolizing enzyme activity may in totality affect the drug clearance and overall drug exposures in burn injury patients [10].

The pathological condition of burn injury has a significant impact on the pharmacokinetic of antibacterial [6]. Several antimicrobials such as

R. P. Dash · R. Rais
Johns Hopkins Drug Discovery Program,
Johns Hopkins University, Baltimore, MD, USA

Department of Neurology, Johns Hopkins University, Baltimore, MD, USA

N. R. Srinivas (✉)
Zydus Research Centre, Ahmedabad, Gujarat, India
e-mail: nuggehally.srinivas@zyduscadila.com

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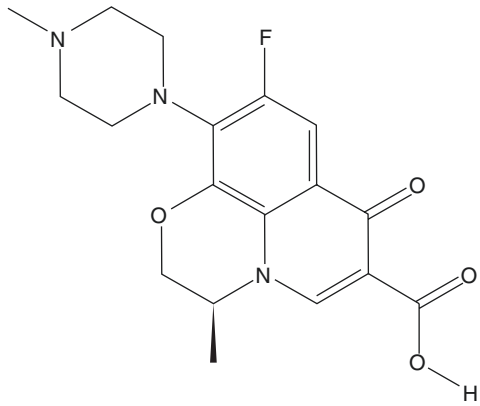


**Fig. 1** Chemical structure of levofloxacin

ciprofloxacin, vancomycin, gentamicin and amikacin have demonstrated significant pharmacokinetic alterations in severely burned patients [11–14]. Burn injury may result in suboptimal dosing and impaired efficacy of the antimicrobial therapies and may result in development of resistance against bacterial pathogens [6]. This requires dose titration to achieve desired efficacy. Keeping in view the significance of antibacterial pharmacokinetics in burn injury patients, this article will focus on understanding the pharmacokinetic aspects of levofloxacin in healthy, diseased and burn injury patients.

## 2 Case Study of Levofloxacin

### 2.1 Levofloxacin Pharmacokinetics in Healthy Subjects

Chow et al. [15] carried out the pharmacokinetic study of levofloxacin administered as 750 mg intravenous infusion once daily for 7 days. The subjects were classified in two groups based on their renal clearance (≤ or ≥80 mL/min). The steady-state plasma concentration was attained in 2 days in all the subjects. However, the maximum plasma concentration ($C_{max}$) and area under the curve (AUC) values of subjects with clearance ≤80 mL/min were 1.6 and 1.8 times higher as compared to the subjects with clearance ≥80 mL/min, thus suggesting that dose adjustments were needed in subjects with higher degree of renal impairment [15]. Multiple-dose intravenous pharmacokinetic study of levofloxacin carried out for 7 days (200 mg single dose on days 1 and 7 and 200 mg twice daily doses from days 2 to 6) in healthy Chinese volunteers resulted in the achievement of steady-state concentration of levofloxacin in 3 days. The half-life was found to be 6 h, and cumulative urinary excretion rate was 88 ± 5%. No significant differences were observed in the AUCs measured on days 1 and 7, thus implying that levofloxacin did not accumulate even after multiple dosing [16]. Nakashima et al. [17] conducted a phase 1 pharmacokinetic study following single (200 mg) and multiple (200 mg given 3 times daily for 7 days) oral dose of levofloxacin under fed condition. The half-life was found to range between 4 and 6 h. Almost, 85–92% of levofloxacin was excreted in urine within 48 h, and a minimal amount of the intact levofloxacin (approximately 4%) was recovered in faeces in 72 h, thus confirming both complete oral absorption of levofloxacin and renal route as the primary path for the elimination of levofloxacin. Furthermore, as noted earlier levofloxacin did not show any accumulation; additionally, lack of chiral conversion of levofloxacin was documented in this study.

### 2.2 Levofloxacin Pharmacokinetics in Special Populations

Madhavi and Priyanka [18] studied the effect of menstrual cycles on the pharmacokinetics of levofloxacin. The findings suggested that the salivary concentration of levofloxacin decreased during the luteal phase owing to the fact that luteal phase exhibits high progesterone levels which in turn induced cytochrome P450 (CYP) enzymes and accelerated the drug metabolism of CYP substrate such as levofloxacin. By the same token, elevated oestrogen levels observed during the follicular stage inhibited the CYP enzymes and resulted in higher salivary levofloxacin concentration [18]. Based on these findings, it was suggested that female subjects may develop resistance towards bacterial infection during the luteal phase [18]. A formal gender effect study observed differences in

the pharmacokinetics of levofloxacin in male versus female subjects [19]. Following a single intravenous dose of levofloxacin (500 mg), the female subjects showed 43 and 23% higher $C_{max}$ and AUC, respectively, as compared to the male counterparts. Although, no significant differences were observed in the half-life, the clearance and volume of distribution in males were 1.3 and 1.5 times higher in male subjects relative to female subjects [19]. Thee et al. [20] described the pharmacokinetic study of levofloxacin in paediatric subjects in three age groups such as 0–2, 2–6 and >6 years, who received body weight adjusted oral dosing of 15 mg/kg of levofloxacin. In this study, no significant differences in the systemic exposure and half-life of levofloxacin were observed amongst the stratified groups. However, the half-life of levofloxacin in the paediatric group was found to be 3 h almost two-fold lower relative to the adult subjects (6 h), conferring a somewhat faster clearance of levofloxacin in paediatric subjects. With respect to the infection status, no significant difference in the pharmacokinetic parameters of levofloxacin was observed between the human immunodeficiency virus (HIV)-infected and HIV-noninfected paediatric subjects [17, 20].

The concentrations of levofloxacin in skin blister fluid relative to those of serum have been reported after a 500 mg oral dose of levofloxacin [21]. The $C_{max}$ of levofloxacin observed for serum samples was approximately two times higher as compared to blister fluid samples. The half-life of levofloxacin appeared to be comparable between the two (8.1 h for serum and 9.2 h for blister fluid). Therefore, this study demonstrated the accessibility of levofloxacin to the deeper tissues and body fluids. Chow et al. [22] observed that levofloxacin (750 mg once daily for 3 days, orally) achieved higher concentrations in the skin tissues as compared to plasma. The tissue/plasma ratio was 1.37 and 1.97 for $C_{max}$ and AUC, respectively. Child et al. [23] conducted a crossover study in six healthy subjects where they received 500 mg of levofloxacin orally every 12 h for five doses in period 1 and 500 mg every 24 h for three doses. No significant difference was found for levofloxacin concentration in plasma and inflammatory fluid collected from the blisters. The overall penetration into inflammatory fluid ranged from 88 to 101% with the 12-h regimen and 83 to 112% with the 24-h regimen. As judged by the mean urinary recoveries of 87 and 86% over the corresponding interval of the 12- and 24-h regimens, respectively, there was no accumulation of levofloxacin.

## 2.3 Levofloxacin Pharmacokinetics in Patients

### 2.3.1 Respiratory Infection

Benko et al. [24] carried out a pharmacokinetic/pharmacodynamic study involving multiples doses of levofloxacin (500 mg, intravenous infusion) in 12 patients with respiratory infections caused by various pathogens. The maximum plasma levofloxacin concentration and the area under the free concentration-time curve for the free fraction of levofloxacin were 8.13 ± 1.64 mg/L and 49.63 ± 15.60 mg h/L, respectively [24].

Boselli et al. [25] conducted a pharmacokinetic study of levofloxacin (500 mg), administered once or twice daily in critically ill patients with severe community-acquired pneumonia. The concentrations of levofloxacin were monitored both in plasma and epithelial lining fluid of the patients. From a pharmacodynamic/clinical perspective, the data demonstrated that the concentrations of levofloxacin exceeded the required minimum inhibitory concentration values of <1 mg/L (serum) and >1 mg/L (epithelial lining fluid) for inhibiting the pathogens. The clearance in the patients dosed once daily was 45.3 mL/min as compared to 40.0 mL/min in patients dosed twice daily, suggesting there was no accumulation of levofloxacin in patients despite multiple dosing of the drug. Pharmacokinetic study following multiple intravenous administration of levofloxacin (1000 mg, once daily) in stable chronic lung disease patients showed significantly higher levofloxacin concentration in the alveolar cells (11.5 times) and epithelial lining fluid (2 times) as compared to the plasma tissue. No significant difference was observed in the half-life for levofloxacin in plasma (8.7 h) and epithelial lining fluid (7 h); however, the half-life of levofloxacin was found to be five to six times

higher for the alveolar cells (49.5 h). The findings of this study indicated that levofloxacin showed deep tissue penetration following a single intravenous dose of 1000 mg once daily and was well tolerated.

Furlanut et al. [26] described the pharmacokinetic study of oral/intravenous levofloxacin in 17 elderly patients suffering from the lower respiratory tract infection. The elderly patients showed slightly longer elimination half-life (9 h) and higher AUC (80 μg h/mL) as compared to healthy subjects who showed a half-life of 6.6 h and AUC of 55.3 μg h/mL [26, 27]. The probable reason for this altered pharmacokinetics of levofloxacin may be due to the declined renal function in the aged patients because 71% of levofloxacin is excreted via renal route [26]. The overall clinical success rate in this study was 94.1% [26]. Noreddin et al. [28] carried out a pharmacokinetic study at three intravenous dose levels; 500, 750 and 1000 mg of levofloxacin in young and elderly patients with community-acquired pneumonia. Younger patients showed higher clearance of levofloxacin (10.4 L/h) as compared to elderly patients (7.4 L/h), whereas the half-life of levofloxacin was longer in elderly patients (9.8 h as compared to younger patients with 7.2 h half-life). Regardless of the three dose levels, the AUC values for levofloxacin were 1.4 times higher in elderly patients (in comparison to younger patients. Based on the AUC/MIC data, 750 mg provided optimum efficacy. An interesting comparative pharmacokinetic study of levofloxacin (500 mg twice daily) in healthy and early-onset ventilator-associated pneumonia (VAP) patients showed a 20–40% lower exposure in patients as compared to healthy individuals [29]. Cumulative urinary excretion during the 12-h dosage interval confirmed the greater excretion of unchanged drug in these patients compared with healthy subjects (76% versus 68%) [29].

### 2.3.2 Miscellaneous

Bellmann et al. [30] observed that inflammatory condition slightly increased the tissue distribution of levofloxacin as compared to normal adipose tissue following single-dose intravenous administration. Interindividual variability in tissue penetration was high, as indicated by a coefficient of variation of approximately 82%. Geller et al. [31] evaluated the pharmacokinetics of levofloxacin (240 mg for 7 days) administered as an aerosol in the patients with cystic fibrosis. The sputum concentration of levofloxacin was 150-fold higher as compared to plasma concentration with no significant difference in time to reach maximum plasma concentration ($T_{max}$). The plasma half-life was 7.49 h as compared to sputum half-life of 4.58 h. Thus, it may be presumed that aerosol delivery system may be considered as a better alternative for treating respiratory infection as compared to oral and intravenous therapies. The patients with cystic fibrosis, although did not show any significant difference in the total clearance, volume of distribution, maximum serum concentration and elimination half-life for levofloxacin (500 mg daily, for 14 days, oral), displayed a rapid attainment of $T_{max}$ as compared to non-cystic fibrotic patients [32]. Rebuck et al. [33] described the pharmacokinetic study of levofloxacin (500 mg once daily) following intravenous and oral administration in critically ill and healthy patients. A 1.2 times higher exposure and lower clearance were observed in patients as compared to healthy subjects. Levofloxacin showed higher penetration to the prostate tissues in acute prostatitis patients undergoing prostatectomies following administration of 500 mg of levofloxacin orally every 24 h for 2 days prior to surgery, and then on the day of surgery, 500 mg was administered as an hour-long, constant-rate intravenous (IV) infusion [34]. The $AUC_{prostate}$:$AUC_{plasma}$ was found to be 2.96 suggesting the efficiency of the penetration of levofloxacin into prostrate tissue for combating infections [34]. Single- and multiple-dose (10 days once daily) oral pharmacokinetic study of levofloxacin (350 mg) in 10 HIV-infected patients did not show any significant difference in the pharmacokinetic parameters except for peak concentrations in plasma, which were 4.79 ± 1.00 and 6.92 ± 1.56 μg/mL for single- and multiple-dose data, respectively, suggesting no accumulation even after multiple dosing and infected condition had no effect on drug clearance [35]. Another study in 30 HIV-infected patients who received 750 mg of drug for 14 days followed with placebo for another

14 days showed that levofloxacin was rapidly absorbed with a maximum plasma concentration ($T_{max}$) of 1.5 h and elimination half-life ranging from 7.2 to 9.4 h [36]. Hutschala et al. [37] observed that the accessibility of levofloxacin (500 mg intravenous) to the cardiac tissues following cardiac surgery was low as observed from the $AUC_{tissue}$:$AUC_{plasma}$ ratio of 0.6. Pharmacokinetic profile of levofloxacin (single dose 500 mg oral) did not change in typhoid patients when compared to that of healthy individuals except 1.3 higher volume of distribution in typhoid patients [38]. Weinrich et al. [39] observed significantly higher liver penetration for levofloxacin (500 mg intravenous) in patients for liver resection. The tissue/serum ratio of levofloxacin was found to be 3.72 at the time of liver resection, thus suggesting that levofloxacin is a good candidate for antibiotic prophylaxis before invasive hepatobiliary procedures [39].

### 2.3.3 Renal Impairment

Bellmann et al. [40] described the pharmacokinetic study of levofloxacin (500 mg intravenous) in 11 critically ill patients who were managed with continuous venovenous infiltration. Out of the 11 patients, 4 patients were on haemofiltration, 4 patients showed moderate renal impairment but were not put on haemofiltration, and 3 had normal renal function. The observed clearance of levofloxacin in patients with normal renal function was comparable to that of healthy subjects. The half-life in renal impaired patients who were not on haemofiltration was 20–25 h which was slightly higher as compared to 30 h as seen in patients on haemofiltration. Thus, levofloxacin dose adjustment was necessary in patients with renal failure without haemofiltration. It was noted that haemofiltration decreased the systemic exposure of levofloxacin and increased the volume of distribution. Malone et al. (2001) also observed that the clearance of levofloxacin was substantially increased during continuous venovenous haemofiltration (CVVH) and continuous venovenous haemodiafiltration (CVVHDF) [41].

Sowinski et al. [42] conducted pharmacokinetic study in noninfected patients with end-stage renal disease upon intravenous infusion (over 1 h) dosing of levofloxacin (250 mg), after a scheduled haemodialysis session [42]. The clearance of levofloxacin reduced to approximately 75% in renal impaired patients. The half-life value of levofloxacin was 35 h in the renal impaired patients and thus supported the need for dose adjustment. The condition of pyelonephritis in women, however, did not have any effect on the elimination of the intravenously administered levofloxacin since the half-life of levofloxacin was found to be 7 h which was comparable to the value observed in healthy male subjects [43]. Additionally, in this study it was confirmed that *E. coli* was completely eradicated from urine within 3–6 h duration following first dose of levofloxacin [43].

Tsaganos et al. [44] determined the effect of intermittent haemodialysis on pharmacokinetics of levofloxacin (500 mg single dose and for 3 days) in patients with end-stage renal disease. Although, the plasma concentration and half-life of levofloxacin was higher in the patients as compared to single dose, the clearance of levofloxacin was equivalent in both the cases, thus indicating no drug accumulation of levofloxacin in patients that were undergoing haemodialysis [44]. A study by Guenter et al. [45] in five renal impaired patients at a dose level of 500 mg/day as an intravenous infusion showed higher clearance of 154 L/h, thus suggesting dose adjustment in renal impaired patients.

### 2.3.4 Levofloxacin Pharmacokinetics in Burn Injury Patients

Kiser et al. [6] conducted a pharmacokinetic study in 11 severe burn injury patients following intravenous dosing of levofloxacin (750 mg, once daily for 4 days). The various pharmacokinetic parameters such as total body clearance, renal clearance, volume of distribution and elimination half-file for levofloxacin were similar between the single intravenous dose (i.e., day 1) and repeated daily intravenous doses (i.e., day 4) of levofloxacin. The mean values of the various pharmacokinetic parameters observed in burn injury patients were similar to the reported values either in healthy subjects or critically ill patients who received similar intravenous doses of levofloxacin. However, one key observation from the

study was the observation of high interindividual variability amongst the burn injury patients. The various pharmacokinetic/pharmacodynamic measures such as minimum inhibitory concentration (MIC)/$C_{max}$ and/or MIC/AUC reported in this study suggested the effectiveness of levofloxacin either used alone and/or in combination with other antibiotics in burn injury patients [6]. Figure 2 shows a comparison of dose-normalized $C_{max}$ and AUC of levofloxacin in healthy subjects with that of burn injury patients, whereas Fig. 3 shows the clearance of levofloxacin in healthy and burn patients. A summary of pharmacokinetic parameters in healthy subjects and patients is shown in Table 1.

## 3 Discussion

The popularity and continued success of levofloxacin as one of the leading fluoroquinolones can be attributed to its favourable safety and tolerability profiles. Furthermore, levofloxacin has demonstrated very impressive pharmacodynamic profile which is accompanied by a consistent and dependable pharmacokinetic behaviour.

On the basis of the review of the pharmacokinetic disposition of levofloxacin, the following deductions can be summarized:

(a) The clinical pharmacokinetics of levofloxacin remained unaltered when single-dose data was compared with multiple-dose data with key parameters such as half-life, clearance and volume of distribution almost indistinguishable suggesting the existence of stationary pharmacokinetics for levofloxacin [46].
(b) The lack of any noticeable disparity between intravenous and oral pharmacokinetics of levofloxacin with almost complete oral bioavailability of the drug was an advantage in making switch decisions between oral and intravenous therapy in the targeted patient population [46].
(c) To a large extent, the existence of similarity in the pharmacokinetics of levofloxacin has been confirmed between healthy human volunteers and intensive care patient population (e.g., respiratory infection), however, with

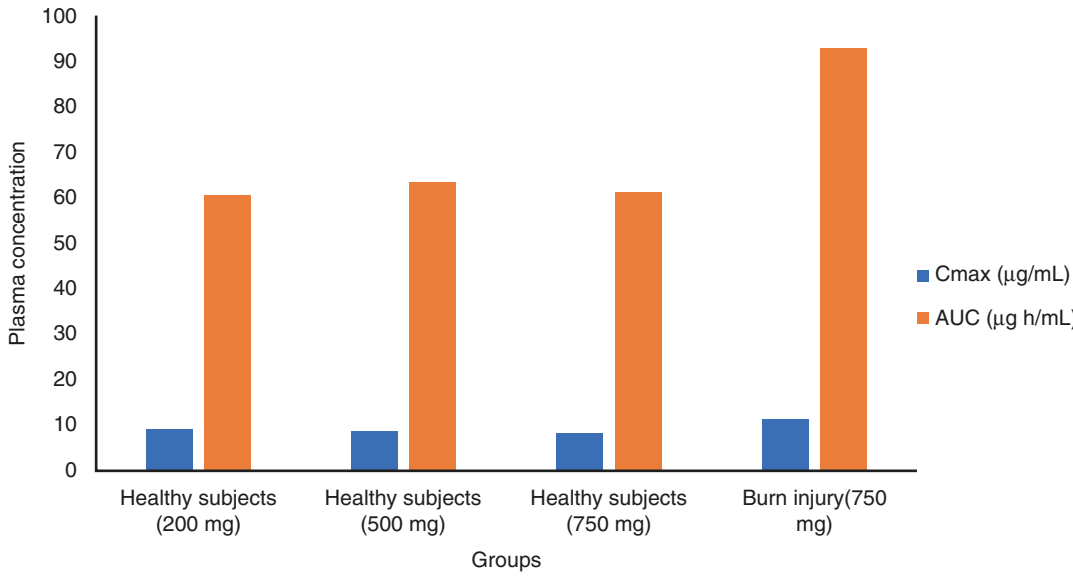


**Fig. 2** Dose-normalized $C_{max}$ and AUC values of levofloxacin in healthy subjects with respect to the dose administered in burn injury patients (750 mg). Data represented for dose levels of 750, 200 and 500 mg in healthy subjects and 750 mg in burn patients corresponds to Refs. [15, 16, 19, 45], respectively

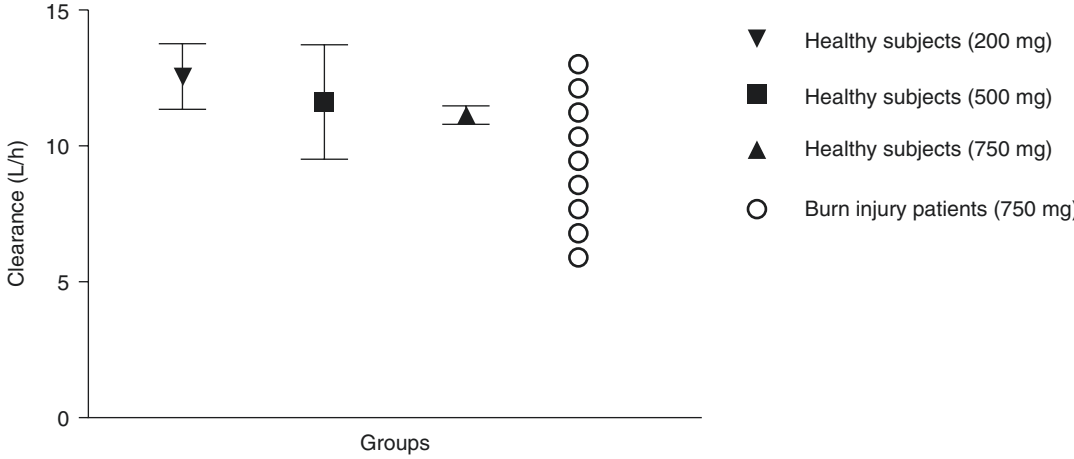


**Fig. 3** Mean (± SD) clearance of levofloxacin in healthy subjects at different dose levels interspersed with the clearance in individual burn injury patients. Data represented for dose levels of 750, 200 and 500 mg in healthy subjects and 750 mg in burn patients corresponds to Refs. [15, 16, 19, 45], respectively

the caveat that any compromised renal function would result in the altered pharmacokinetics of levofloxacin which may have to be factored in proper dosing decisions [15, 33].

(d) The lack of the effect of either sex or age on the pharmacokinetics of levofloxacin in healthy subjects that have uncompromised renal function should be advantageous in treating disease population at large [47].

(e) The penetration of levofloxacin to body fluids (i.e., blister fluid), tissues of interest and respiratory cavities was shown to be adequate for levofloxacin to exhibit its promising pharmacodynamic activity [25, 34, 48, 49].

On the topic of drug-drug interaction liability of levofloxacin as either a perpetrator or a victim, a few studies have been published. Chien [46] showed that the pharmacokinetic profile of levofloxacin in HIV-infected patients was not altered by the concomitant administration of zidovudine; by the same token, the pharmacokinetics of zidovudine pharmacokinetics was unaffected by levofloxacin. Lee et al. [50] showed that co-administration of sucralfate, approximately 2 h post oral levofloxacin administration, had no bearing on the absorption and overall disposition of levofloxacin, and therefore, the non-inclusion of sucralfate was not considered essential in levofloxacin therapy. The co-administration of levofloxacin with other fluoroquinolones such as ciprofloxacin, norfloxacin and ofloxacin slightly increased the exposure by 10–17% [51]. The addition of levofloxacin to the steady-state regimen of theophylline marginally increased the serum concentration of theophylline [52]. Studies carried out with several oral antacid preparations such as aluminium or magnesium hydroxide preparations suggested that levofloxacin absorption and exposure was significantly affected by the simultaneous intake of levofloxacin with antacid preparations [53]. However, a 2-h window, either before or after levofloxacin dosing, was necessary, to permit the intake of antacids without any altered pharmacokinetics of levofloxacin [53]. Co-administration of cimetidine and probenecid resulted in the alteration in the pharmacokinetic profile of levofloxacin with respect to increased exposure and half-life by approximately 30–38% [54].

One important consideration is that how to put the various pharmacokinetic data of levofloxacin including drug-drug interaction potential in the context of burn injury patients. Although generally it appeared that pharmacokinetic parameters of levofloxacin were similar between burn injury patients and other studied population, there may be some situations of either a faster or slower clearance of levofloxacin that need to be anticipated in the therapy. One important caveat that

**Table 1** Tabulated summary of clinical study design, objectives and pharmacokinetic data of levofloxacin in human studies

| Study particulars | Pharmacokinetic data | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Subjects/design | Type | $C_{max}$ (μg/mL) | $T_{max}$ (h) | $t_{1/2}$ (h) | AUC (μg h/mL) | CL or CL/F (L/h) | $V_d$ (L) | Remarks [Ref.] |
| *Healthy* | | | | | | | | |
| $N = 18$ (M and F); randomized, double-blind, placebo-controlled | Clearance >80 mL/min ($N = 4$) | | | 6.91 | | 11.16 | 106.0 | Levofloxacin was found to be well tolerated even after multiple dosing at 750 mg [15] |
| Single-centre, parallel group study. Subjects were classified in two groups based on creatinine clearance | Single dose Day 1 | 8.12 | – | | 61.1 | | | |
| | Steady state Day 10 | 8.71 | – | | 67.4 | | | |
| Levofloxacin 750 mg administered as IV infusion on day 1. Days 2 and 3, no treatment. Days 4–10, 7 once-daily IV infusions were administered | Clearance ≤80 mL/min ($N = 8$) | | | 7.82 | | 6.42 | 69.0 | |
| | Single dose Day 1 | 12.9 | | | 121.0 | | | |
| | Steady state Day 10 | 14.2 | – | | 139.0 | | | |
| $N = 10$ M multiple-dose, open-label, single-centre study | Plasma profile | | | | | | | No accumulation of levofloxacin was observed after multiple dosing for 7 days [16] |
| Levofloxacin (200 mg) was administered once on days 1 and 7 and twice from days 2 to 6 as IV infusion | Day 1 | 2.4 | – | 6.3 | 16.1 | 12.6 | 33.0 | |
| | Day 7 | 2.9 | – | 6.2 | 23.0 | 9.3 | 39.0 | |
| $N = 5$; 1 period, single centre Levofloxacin (200 mg) was given thrice daily after meal | Plasma profile | 2.04 | 1.48 | 5.97 | 19.88 | – | 1.25 | No accumulation or chiral conversion of levofloxacin was observed after multiple dosing and was found to be well tolerated [17] |
| $N = 15$, F; single-centre study | Follicular phase | 128.4 | 1.0 | 9.93 | 1239.0 | 6.8 | 104.0 | Systemic exposure of levofloxacin was higher during the follicular phase [18] |
| Subjects received levofloxacin 500 mg, on days 10 (follicular phase) and 21 (luteal phase) of menstrual cycle | Luteal phase | 76.8 | 1.0 | 4.59 | 255.1 | 18.7 | 150 | |
| $N = 20$ (11M, 9F); open-label, single-centre study | Men | 5.66 | – | 7.69 | 42.13 | 11.67 | 120.35 | Systemic exposure level of levofloxacin was higher in women as compared to men [19] |
| Dose was 500 mg single-dose intravenous | Women | 8.10 | – | 6.47 | 54.27 | 9.05 | 79.27 | |
| $N = 22$ paediatric subjects, single-centre study, HIV infected and 18 noninfected | Age group | | | | | | | HIV status and age did not have any effect on the pharmacokinetic profile of levofloxacin in paediatric subjects [20] |
| Single-oral dose of levofloxacin (15 mg/kg) dosed under fasted condition | 0–2 years | 7.0 | 1.33 | 1.79 | 29.89 | – | – | |
| | 2–6 years | 6.86 | 1.56 | 3.22 | 31.69 | – | – | |
| | ≥6 years | 4.98 | 1.50 | 3.37 | 27.49 | – | – | |
| | HIV status | | | | | | | |
| | Infected | 4.98 | 1.50 | 3.37 | 27.49 | – | – | |
| | Noninfected | 6.88 | 1.44 | 3.09 | 31.38 | – | – | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| *N* = 20 M, single-centre study | Serum | 6.92 | 1.75 | 8.10 | 42.64 | 10.8 | 114.3 | Levofloxacin was well tolerated and showed good tissue penetration [21] |
| Levofloxacin (500 mg) was administered as a single oral dose | Skin blister fluid | 3.61 | 4.10 | 9.21 | 47.61 | – | – | |
| *N* = 10 M; non-comparative, open-label, single-centre, randomized, phase I study<br>Levofloxacin (750 mg) was dosed once daily for 3 days | Plasma | 8.99 | 1.1 | 8.23 | 82.0 | 9.43 | 105.0 | Tissue/plasma ratio was found to be 1.97 suggesting penetration of levofloxacin to deep tissues [22] |
| | Tissue[a] | 11.77 | 3.3 | – | 161.0 | – | – | |
| *N* = 6 M; open-label crossover study<br>Subjects received 500 mg of levofloxacin orally every 12 h for five doses or 500 mg every 24 h for three doses, and then 6 weeks later, they received the other course | Plasma | | | | | | | Levofloxacin showed higher penetration to the inflammatory tissues [23] |
| | 500 mg every 24 h | 6.55 | 1.17 | 7.95 | 53.5 | 9.69 | 66.4 | |
| | 500 mg every 12 h | 9.53 | 1.08 | 7.91 | 60.0 | 8.92 | 69.8 | |
| | Skin blister fluid | | | | | | | |
| | 500 mg every 24 h | 4.33 | 3.67 | 7.95 | 54.1 | 20.9 | 35.2 | |
| | 500 mg every 12 h | 6.79 | 2.33 | 7.91 | 55.9 | 29.7 | 27.7 | |
| *Respiratory infection* | | | | | | | | |
| *N* = 14; open-label study<br>Levofloxacin (2 × 500 mg on day 1 and 1 × 500 mg from days 2 to 7) was administered as an IV infusion | Plasma profile | 8.13 | – | 6.23 | 49.63 | 10.68 | 85.35 | Levofloxacin was found to be effective in critically ill patients [24] |
| *N* = 24 patients with severe community-acquired pneumonia<br>All subjects received 1-h intravenous infusions of 500 mg levofloxacin once or twice daily | Plasma | | | | | | | Levofloxacin exhibited excellent extracellular lung penetration of greater than 100% and a wide interindividual pharmacokinetic variability [25] |
| | 500 mg once daily | 12.6 | 0.2 | 11.5 | 151.0 | 45.3 | 41.0 | |
| | 500 mg twice daily | 19.7 | 0.3 | 17.0 | 208.0 | 40.0 | 55.5 | |
| | Epithelial lining fluid | 11.9 | – | – | – | – | – | |
| *N* = 16 subjects with chronic lung disease<br>Levofloxacin 1000 mg was administered once daily for 3 days | Plasma | 9.4 | 4.0 | 8.7 | 130.0 | – | – | Levofloxacin showed deep tissue penetration at a single intravenous dose of 1000 mg once daily and well tolerated [48] |
| | Epithelial lining fluid | 22.8 | 4.0 | 7.0 | 260.0 | – | – | |
| | Alveolar cells | 76.3 | 4.0 | 49.5 | 1492.0 | – | – | |
| *N* = 17 (10M, 7F); patients with lower respiratory tract infection<br>Levofloxacin 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) | IV | 10.71 | – | 8.77 | 74.97 | 112.2 | 88.04 | Levofloxacin exhibited more than 99% absolute oral bioavailability and clinical success rate of 94.1% [26] |
| | Oral | 7.93 | 1.23 | 9.91 | 85.60 | 99.0 | 87.33 | |

(continued)

**Table 1** (continued)

| Study particulars | Pharmacokinetic data | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Subjects/design | Type | $C_{max}$ (μg/mL) | $T_{max}$ (h) | $t_{1/2}$ (h) | AUC (μg h/mL) | CL or CL/F (L/h) | $V_d$ (L) | Remarks [Ref.] |
| $N = 138$ elderly and $N = 45$ young patients with CAP<br>Levofloxacin was administered as 500, 750 and 1000 mg single IV dose | Plasma | | | | | | | Based on the AUC/MIC data, 750 mg provided optimum efficacy [28] |
| | Elderly patients | | | 9.8 | | 7.2 | 62.91 | |
| | 500 mg | – | – | | 49.9 | | | |
| | 750 mg | – | – | | 74.8 | | | |
| | 1000 mg | – | – | | 99.7 | | | |
| | Young patients | | | 7.4 | | 10.4 | 68.22 | |
| | 500 mg | – | – | | 34.8 | | | |
| | 750 mg | – | – | | 52.3 | | | |
| | 1000 mg | – | – | | 69.7 | | | |
| | Epithelial lining fluid | | | | | | | |
| | Elderly patients | | | | | | | |
| | 500 mg | – | – | | 57.8 | | | |
| | 750 mg | – | – | | 86.7 | | | |
| | 1000 mg | – | – | | 115.7 | | | |
| | Young patients | | | | | | | |
| | 500 mg | – | – | | 40.4 | | | |
| | 750 mg | – | – | | 60.7 | | | |
| | 1000 mg | – | – | | 80.9 | | | |
| $N = 10$ patients (8M, 2F) with early-onset ventilator-associated pneumonia<br>Levofloxacin 500 mg was dosed twice daily for 8 days | Plasma | 8.19 | – | 0.22 | 33.90 | 204.0 | 98.82 | Intravenous levofloxacin 500 mg twice daily was found to be suitable in the treatment of early-onset VAP in ICU patients with normal renal function [29] |
| *Renal impairment* | | | | | | | | |
| $N = 11$ patients and 2 controls, single-centre study<br>Patients were classified as group 1, undergoing CVVH; group 2, NO CVVH, creatinine clearance ≥1.5 mg/dL; and group 3, NO CVVH, creatinine clearance ≤1.5 mg/dL. Dose of levofloxacin was 500 mg, intravenously administered | Group 1 | 4.9 | – | 28.7 | 34.9 | 15.9 | – | Patients with normal renal function showed equivalent clearance as compared to healthy subjects. However, renal impaired patient showed longer half-life and delayed clearance [40] |
| | Group 2 | 6.8 | – | 4.2 | 46.5 | 7.61 | – | |
| | Group 3 | 8.7 | – | 20.6 | 25.5 | 10.21 | – | |
| | Control | 7.9 | – | 7.7 | 40.5 | 8.23 | – | |
| $N = 5$ critically ill patients undergoing CVVHDF and CVVH; single-centre study<br>Patients received levofloxacin 500 mg/day. All patients received CVVHDF on day 1 and CVVH on day 2 | Plasma profile | 9.04 | – | 28.8 | 153.6 | 54.04 | 1.51 | Dose adjustment is required in patients with renal impairment [45] |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| *N* = 8 female subjects with acute nonobstructive pyelonephritis<br>Levofloxacin (750 mg) dosed intravenously once daily for 5 days | Plasma | 12.5 | 1.0 | 6.7 | 85.4 | – | – | Levofloxacin was well tolerated and exhibited optimum efficacy [43] |
| *N* = 8 patients with end-stage renal disease undergoing haemodialysis<br>Levofloxacin (250 mg) was dosed over 1 h as infusion after a scheduled haemodialysis session | Serum | 5.15 | – | 34.4 | 44.6 | 37.0 | 103.3 | Optimum $C_{max}$-AUC ratio was obtained following 250 mg doses for 5 days [42] |
| *N* = 10 patients undergoing haemodialysis. Single-centre, 2-week washout period<br>Phase 1: Single dose levofloxacin (500 mg), orally<br>Phase 2: 500 mg for 3 consecutive days, orally | Single dose plasma profile | 5.04 | 1.50 | 22.84 | 144.96 | 2.67 | 109.47 | Levofloxacin showed accumulation following multiple dosing in patients with renal impairment, thus requiring dose titration [44] |
| | Multiple dose plasma profile | 8.32 | 52.0 | 38.05 | 542.26 | 2.10 | 131.19 | |
| *Miscellaneous* | | | | | | | | |
| *N* = 6 patients with soft tissue injury<br>Levofloxacin (500 mg) dosed once, intravenously | Plasma | 8.73 | 0.52[b] | 10.0 | 32.3 | 9.57 | 107.61 | Levofloxacin exhibited deep tissue penetration. No significant difference was observed in levofloxacin concentration in healthy and inflamed tissue [30] |
| | Inflamed tissue | 5.45 | 1.06[b] | – | 25.5 | – | – | |
| | Healthy tissue | 4.42 | 1.39[b] | – | 23.5 | – | – | |
| *N* = 10 patients with cystic fibrosis<br>Levofloxacin (240 mg) administered as inhaler once daily for 7 days | Plasma | 1.71 | 0.34 | 7.49 | 14.77 | – | – | Significant concentration of levofloxacin was attained in sputum samples following administration via nasal route [31] |
| | Sputum | 4691 | 0.29 | 4.58 | 4507 | – | – | |
| *N* = 10 HIV-infected patients; phase I, double-blind, randomized study<br>Levofloxacin (350 mg) was administered orally once on day 1. From days 3 to 10, levofloxacin (350 mg) was dosed thrice daily | Single dose (day 1) | 4.79 | 1.0[b] | 5.66 | 29.94 | 12.30 | 98.76 | Levofloxacin did not show any accumulation following multiple-dosing regimen [35] |
| | Multiple dose (day 10) | 6.92 | 0.90[b] | 6.50 | 31.24 | 11.18 | 104.10 | |
| *N* = 6 in patients undergone cardiac surgery<br>Levofloxacin 500 mg administered intravenously | Plasma[c] | 15.9 | 0.33 | – | 32.6 | – | – | Levofloxacin showed penetration to the lung tissue with tissue/plasma ratio of 0.6 [37] |
| | Tissue[c] | 6.8 | 0.67 | – | 18.6 | – | – | |
| *N* = 22 (12 patients with cystic fibrosis and 10 non-cystic fibrotic subjects)<br>Levofloxacin (500 mg) dosed orally q.d. for 14 days | Cystic fibrotic patient | 7.06 | 2.20 | 6.44 | 71.32 | 130.2 | 70.6 | Systemic exposure of levofloxacin was 1.5 times higher in cystic fibrotic patients as compared to their normal counterparts [32] |
| | Non-cystic fibrotic subjects | 5.72 | 1.10 | 6.81 | 47.5 | 174.5 | 102.0 | |
| *N* = 9 Caucasian ICU patients<br>Levofloxacin (500 mg) administered as infusion<br>Assessment | Plasma | 8.43 | – | 13.01 | 110.29 | 6.57 | 101.38 | Pharmacokinetic profile of levofloxacin ICU patients was similar to that of healthy subjects [55] |

(continued)

**Table 1** (continued)

| Study particulars | Pharmacokinetic data | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Subjects/design | Type | $C_{max}$ (μg/mL) | $T_{max}$ (h) | $t_{1/2}$ (h) | AUC (μg h/mL) | CL or CL/F (L/h) | $V_d$ (L) | Remarks [Ref.] |
| *N* = 12 (6 healthy and 6 typhoid patients) Levofloxacin (500 mg) dosed once orally | Healthy | 7.57 | 1.87 | 11.15 | 106.23 | 4.76 | 76.36 | No significant difference was observed in the pharmacokinetic profile of levofloxacin in healthy subjects and typhoid patients [38] |
| | Typhoid patients | 7.59 | 1.82 | 10.02 | 102.38 | 4.89 | 70.43 | |
| *N* = 28 critically ill patients (18 with normal hepatic function and 10 with hepatic dysfunction); open-label study Levofloxacin (500 mg) administered intravenously for 5 days | Normal hepatic function | 7.5 | – | 7.6 | 61.0 | 135 | 93.5 | Hepatic dysfunction had no effect on the disposition of levofloxacin [33] |
| | Hepatic dysfunction | 7.4 | – | 8.7 | 67.9 | 132 | 98.3 | |
| *Burn injury* | | | | | | | | |
| *N* = 10 severely burned ICU patients Levofloxacin (750 mg) dosed as infusion | Plasma profile | 11.3 | – | 7.8 | 93.0 | 9.0 | 101.2 | Pharmacokinetic profile of levofloxacin in burn injury patients was similar to that of critically ill patients. Higher inter-patient variability was observed in burn injury subjects [6] |
| *Drug-drug interaction* | | | | | | | | |
| *N* = 6 HIV-infected patients Levofloxacin (350 mg, orally) was dosed once on days 1 and 10 and thrice a day from days 3 to 9. Zidovudine (100 mg, orally) dosed once on days 1 and 10 | Day 1 | 3.82 | 1.0 | 6.2 | 17.2 | 11.4 | 98.0 | No pharmacokinetic interaction was observed [46] |
| | Day 10 | 7.06 | 1.1 | 7.2 | 37.4 | 9.4 | 109.0 | |
| *N* = 24 (12M, 2F), single-dose, open-label, randomized crossover study Levofloxacin (500 mg) was administered alone and in combination with 1000 mg sucralfate under fasted condition | Levofloxacin alone | 5.9 | 1.0 | 6.2 | 50.5 | 10.1 | – | Sucralfate did not affect the pharmacokinetics of levofloxacin [50] |
| | Levofloxacin + sucralfate | 6.7 | 1.0 | 6.1 | 47.9 | 10.7 | – | |

Data expressed as mean for all parameters except for $t_{max}$ which are expressed as median

*HV* human volunteers, *M* male, *F* female

[a]Values expressed as median

[b]Tissue concentration expressed as μg/g

[c]$T_{max}$ expressed as mean

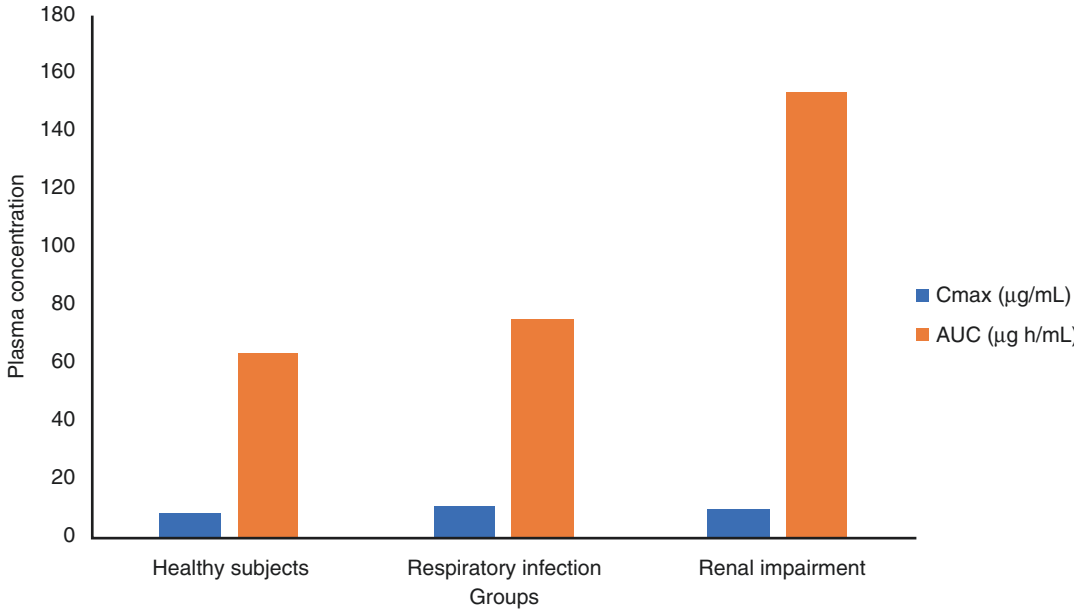


**Fig. 4** Dose-normalized $C_{max}$ and AUC values of levofloxacin in healthy subjects and renal impaired patients with respect to the dose administered in respiratory infection patients (500 mg). Data represented for healthy subjects, respiratory infection and renal impaired patients corresponds to Refs. [6, 19, 26], respectively

needs to be considered is that if burn injury patients have an underlying renal impairment issue, it is quite possible that levofloxacin pharmacokinetics will likely be altered and consideration of dose adjustment in such patients would become critical. Another observation worthy of discussion is the high degree of variability in the inter-patient pharmacokinetics of levofloxacin in the burn injury patients. As pointed out earlier, burn injury has the potential to alter several physiological process key for the drug disposition, which in turn contributes for the observed variability. Such high degree of variability in burn injury patients was not unique for levofloxacin but has been also reported for other antibiotics such as vancomycin, ciprofloxacin, etc. [11, 12]. From the drug-drug interaction perspective, only thing of relevance was with respect to the observed pharmacokinetic interaction between levofloxacin and cimetidine/probenecid. Because both probenecid and cimetidine interfere in the renal excretory process of levofloxacin, they tended to decrease the excretion of levofloxacin and increase its half-life and exposure. Hence, as a precautionary measure for treating burn injury patients with levofloxacin, other co-medications that influence the urinary excretory processes should be replaced with other agents that will not interfere in the urinary excretory process of levofloxacin (Fig. 4).

Despite the high degree of variability in the pharmacokinetic parameters of levofloxacin in burn injury patients, a simple linear regression model was proposed to predict the pharmacokinetics of levofloxacin with a limited sampling strategy [5]. Furthermore, the developed linear regression model using pharmacokinetic data in burn injury patients was also shown to be applicable for the prediction of levofloxacin pharmacokinetics in healthy subjects who were dosed either orally or intravenously [5].

## Conclusions

The focus of the review was to provide a comprehensive report on the pharmacokinetics of levofloxacin in healthy subjects, critical care patients and burn injury patients. In addition to describing the general clinical pharmacokinetics of levofloxacin across the population spread, other important factors that may play a

role in the pharmacokinetics of levofloxacin such as age, sex, renal impairment status, etc. have been summarized. Based on the review, levofloxacin showed comparable pharmacokinetics across the varied population including burn injury patients. The burn injury patients tended to exhibit higher degree of pharmacokinetic variability. Regardless of the population, renal function status was shown to alter the pharmacokinetics of levofloxacin. Therefore, dose adjustment decision of levofloxacin in burn injury patients and/or critical care patients should consider the renal function. Another important consideration in clinical therapy with levofloxacin was to examine the probable role of co-medication on the renal functionality in burn injury or critical care patients who were stabilized with an appropriate dose of levofloxacin.

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