

# Pharmacokinetics of Moxifloxacin and Levofloxacin in Intensive Care Unit Patients Who Have Acute Renal Failure and Undergo Extended Daily Dialysis

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Extended daily dialysis (EDD) is increasingly popular in the treatment of acute renal failure (ARF). EDD could remove drugs to a much different degree compared with intermittent standard hemodialysis or continuous renal replacement therapies; however, there are only scarce data on how EDD influences the pharmacokinetics of frequently used drugs. The aim of this study was to determine the pharmacokinetics of two quinolone antibiotics in patients who had anuric ARF and were being treated with EDD. Adult patients who were in the intensive care unit at a tertiary care university hospital and receiving moxifloxacin ( $n = 10$ ) or levofloxacin ( $n = 5$ ) therapy were included. The antibiotics were administered intravenously 8 h (400 mg of moxifloxacin) or 12 h (500 mg of levofloxacin) before EDD to study pharmacokinetics off and on EDD. Treatment lasted 8 h; blood and dialysate flow rates were 160 ml/min. In addition to standard pharmacokinetic parameters, the total dialysate concentration of both drugs was measured using a technically simple single-pass batch dialysis system for EDD. Moxifloxacin pharmacokinetics in critically ill patients who had ARF and were undergoing EDD were similar to those in healthy subjects without renal impairment. Levofloxacin, although removed by EDD, had a lower total clearance compared with healthy subjects. According to these findings, anuric critically ill patients who are undergoing EDD should be treated with the standard dosage of moxifloxacin (400 mg/d intravenously). The levofloxacin dosage, however, should be reduced according to the intensity of renal replacement therapy.

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Fluoroquinolones have enjoyed enormous clinical success in the past 20 yr. The most widely used group II fluoroquinolones (ciprofloxacin and ofloxacin) exhibit activity mainly against Gram-negative bacteria. Recently, group III (levofloxacin) and group IV (moxifloxacin) fluoroquinolones, which possess an improved activity against Gram-positive pathogens while maintaining similar activity against many Gram-negative bacteria, increasingly have been used (1).

In intensive care unit (ICU) patients who have sepsis and multiple organ failure, extended daily dialysis (EDD) represents an important extracorporeal renal replacement therapy that is increasingly used in ICU throughout Europe, the United States, and Brazil (2–8). EDD could remove drugs to a much different degree compared with standard intermittent hemodialysis (IHD) three times a week or continuous renal replacement therapy (CRRT) (9). Nevertheless, only scarce data are

available on the effect of this highly efficient renal replacement therapy on the elimination of frequently used drugs in critically ill patients with renal failure (10–13). The aim of our study was to investigate the pharmacokinetics of moxifloxacin and levofloxacin in anuric critically ill patients who were undergoing EDD. Because there is no reliable standard approach, we applied various methods to estimate extracorporeal drug removal.

## Materials and Methods

### Patients and Study Protocol

Adult ICU patients who had anuric acute renal failure (ARF) and were being treated with EDD and receiving either moxifloxacin ( $n = 10$ ) or levofloxacin ( $n = 5$ ) were enrolled. The choice of the antibiotic for each patient was made on clinical grounds. Patients were included into the study after informed consent had been obtained from the patient or the patient's legal representative. Moxifloxacin (400 mg) was infused intravenously in 10 patients during a period of 60 min, 8 h before EDD was started. Because the plasma half-life of levofloxacin in renal failure is known to be substantially increased, levofloxacin (250 or 500 mg) was infused during a period of 60 min even 12 h before EDD was started. This approach was chosen to study the pharmacokinetics of the two drugs off and on dialysis in the same patient while avoiding interday variability. The study protocol was approved by the Hannover Medical

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School Ethics Committee (project #2698) and was conducted in accordance with the Declaration of Helsinki and German federal guidelines.

EDD was performed using the GENIUS batch dialysis system (Fresenius Medical Care, Bad Homburg, Germany) with a polysulfone high-flux dialyzer (F60S, surface area 1.3 m<sup>2</sup>; Fresenius Medical Care) as described previously (14,15). The technical details of the system are explained elsewhere (16). In brief, sterile bicarbonate dialysate is filled into a 75-L tank and subsequently is circulated in a closed-loop circuit. During dialysis, fresh dialysate is taken from the top of the tank while the spent dialysate flows back to the bottom. Complete collection of spent dialysate in the same tank after the dialysis session permits estimation of the total amount of a substance that is removed, assuming that adsorption of the substance to the dialyzer system is negligible. The average dialysis time during the study was 481 ± 9 min, and mean blood and countercurrent dialysate flow was 161 ± 4 ml/min. Vascular access in all patients was achieved by a double-lumen catheter inserted either into the internal jugular or into the femoral vein.

Blood samples were drawn from the arterial line placed in the radial or femoral artery before as well as 0.5, 1, 2, 4, 6, and 8 h after administration of moxifloxacin or levofloxacin. In the case of levofloxacin, an additional blood sample was obtained 12 h after administration of the drug. Additional blood samples were drawn before and during dialysis at time points 2, 4, and 6 h; at the end of dialysis; and 0.5, 1, 3, and 8 h after the end of the EDD treatment. Extra blood samples were drawn before and after dialyzer (*i.e.*, from the afferent “artery” and efferent “venous” dialyzer blood tubing) to calculate the dialyzer clearance from the pre- and postdialyzer concentration difference and the estimated plasma flow. In addition, total drug removal was estimated by measurement of drug concentration in the spent dialysate, because the GENIUS system permits easy access to the entire used dialysate (16).

### Chemical Assays

Moxifloxacin plasma concentrations were determined by HPLC with fluorometric detection similar to a previously described method (17). Shortly, an internal standard was added to 100 μl of plasma or dialysate. After protein precipitation of the sample, liquid chromatography and fluorescence detection were performed using an HP 1090 instrument (Hewlett-Packard, Waldbronn, Germany), equipped with a fluorescence detector (HP 1046 A; excitation at 296 nm and emission at 504 nm for all analyses). The autosampler temperature was kept at 8°C using a Haake D 8 water bath. A Nucleosil 100 C<sub>18</sub> (5-μm particle size, 200 × 2.0 mm ID) capillary column preceded by a guard column (20 × 2.0 mm ID) was used for separation. The column oven temperature was set to 50°C. The mobile phase consisted of an aqueous solution of 0.01 mol/L tetrabutyl ammonium sulfate and 0.05 M sodium dihydrogen phosphate. The flow rate was set at 1.1 ml/min for the separation. The limit of quantification was 10 μg/L. Quality control samples that were produced from blank plasma and dialysate that was spiked with known concentrations of the drug (0.03, 0.5, and 4.0 mg/L) were stored and analyzed together with the study samples. The linear working range of the analytical assay was between 0.025 (lower limit of quantification) and 5 mg/L (upper limit of quantification).

Levofloxacin plasma concentrations also were determined by HPLC with fluorometric detection as described previously (18). Briefly, serum samples that were spiked with the internal standard ciprofloxacin (Bayer Pharmaceuticals, Leverkusen, Germany) were prepared by protein precipitation using a precipitation reagent that consisted of water, methanol, perchloric acid 70%, and orthophosphoric acid (500:500:10:1 vol/vol/vol/vol). After centrifugation (7826 × g, 10 min, 10°C) 20 μl of the supernatant was applied to the analytical column (Waters Symmetry column C<sub>18</sub> 5 μm, 150 × 4.6 mm; Eschborn, Germany). The mobile phase consisted of water, methanol, triethylamine, and orthophospho-

ric acid (750:250:4:2.5 vol/vol/vol/vol). All analyses were performed at room temperature. The fluorescence detector (Perkin Elmer, Überlingen, Germany) was set at excitation and emission wavelengths of 295 and 490 nm, respectively. At a flow rate of 1.5 ml/min, the retention times of levofloxacin and ciprofloxacin were 4.3 min and 6.0 min, respectively.

The calibration curve was linear over the usable concentration range from 0.1 to 40 mg/L. The intra- and interday coefficients of variation were determined using 1, 4, and 8 mg/L levofloxacin and were <5%. Limit of quantification was determined as 0.01 mg/L, and the limit of detection was 0.001 mg/L.

### Pharmacokinetic Calculations

Pharmacokinetic parameters of moxifloxacin and levofloxacin on and off EDD were estimated by noncompartmental methods. The half-life on (T<sub>1/2on</sub>) and off (T<sub>1/2off</sub>) EDD was estimated from the concentration decline during and after EDD. The drug clearance without EDD was calculated as CL<sub>off</sub> = D/AUC<sub>off</sub> (dose/area under the curve [AUC]). In the case of a first dose, the AUC<sub>off</sub> was extrapolated from the beginning of EDD to infinity using T<sub>1/2off</sub>. In the case of steady-state conditions after multiple doses (two patients in the levofloxacin group had received levofloxacin over 9 d before the study), the AUC<sub>off</sub> was extrapolated to the end of the individually applied dosage interval disregarding EDD. The apparent volume of distribution was estimated as V<sub>d</sub> = CL<sub>off</sub> × T<sub>1/2off</sub>/ln(2).

Because there is no standard approach, we applied five methods to estimate drug removal by hemodialysis. In method 1, the dialysis clearance was calculated from the area under the curve during EDD (AUC<sub>EDD</sub>), the drug concentration (C<sub>dial</sub>), and amount of dialysate (V<sub>dial</sub>) as CL<sub>dial</sub> = C<sub>dial</sub> × V<sub>dial</sub>/AUC<sub>EDD</sub>. In method 2, the dialysis clearance was estimated from concentrations before (C<sub>in</sub>) and directly after (C<sub>out</sub>) the dialysis membrane as CL<sub>dial</sub> = (F<sub>in</sub> × C<sub>in</sub> - F<sub>out</sub> × C<sub>out</sub>)/C<sub>in</sub>, where the plasma flow in (F<sub>in</sub>) and out (F<sub>out</sub>) of the dialyzer was estimated using the blood flow, hematocrit, and ultrafiltration rate. In method 3, the fraction of drug removed by one EDD was calculated as fract<sub>D</sub> = 1 - exp(-CL<sub>dial</sub> × T<sub>EDD</sub>/V<sub>d</sub>), where T<sub>EDD</sub> is the time on EDD and CL<sub>dial</sub> as derived by method 1 was applied. In method 4, the removed fraction was derived from the half-life on and off EDD as fract<sub>D</sub> = (1 - exp[-ln(2) × T<sub>EDD</sub>/T<sub>1/2on</sub>]) × (T<sub>1/2off</sub> - T<sub>1/2on</sub>)/T<sub>1/2off</sub>. In method 5, the removed fraction was estimated using the AUC as fract<sub>D</sub> = (AUC<sub>withoutEDD</sub> - AUC<sub>withEDD</sub>)/AUC<sub>withoutEDD</sub>, as described previously (19). It should be noted that the dialysis clearance is an estimate of the extracorporeal clearance by the dialysis system. The total drug clearance during dialysis could be estimated by adding CL<sub>off</sub> and CL<sub>dial</sub>. All pharmacokinetic calculations were performed with the help of the software WinNonlin Professional 4.0.1 (Pharsight Corp., Mountain View, CA) and Excel 2000 (Microsoft Corp., Seattle, WA).

### Results

The patient demographic and clinical information is given in Tables 1 and 2. Median serum concentration time data for moxifloxacin and levofloxacin are shown in Figures 1 and 2.

The moxifloxacin clearance off dialysis was 15.7 L/h (range 8.1 to 49.3 L/h), resulting in a half-life of 12.3 h (range 3.7 to 34.0 h). Because the dialysis procedure itself added a clearance of 2.0 to 3.1 L/h, the half-life of moxifloxacin during dialysis was reduced to 6.0 h (range 3.9 to 11.0 h).

The levofloxacin clearance off dialysis was 3.07 L/h (range 2.96 to 3.17 L/h), resulting in a half-life of 34.5 h (range 21.2 to 47.7 h). Because the dialysis procedure itself added a clearance

Table 1. Demographic of the studied critically ill patients who were treated with moxifloxacin and EDD<sup>a</sup>

| Patient | Gender | Age | BMI  | Main Diagnosis   |
|---------|--------|-----|------|--|
| 1       | M      | 54  | 22.8 | Aspiration pneumonia, hemochromatosis, Child-Pugh class B                |
| 2       | M      | 25  | 15.9 | Pneumonia, hepatic cell carcinoma, hepatitis C, Child-Pugh class C       |
| 3       | F      | 58  | 26.6 | Status post liver transplantation, hepatitis B and C, Child-Pugh class C |
| 4       | M      | 76  | 25.6 | Peritonitis, appendicitis  |
| 5       | M      | 76  | 25.1 | Resection of esophagus, stomach cancer                                   |
| 6       | M      | 49  | 21.3 | Liver cirrhosis, esophageal bleeding, Child-Pugh class C                 |
| 7       | M      | 47  | 22.4 | Liver transplantation, hepatitis B/D, Child-Pugh class C                 |
| 8       | M      | 62  | 25.2 | Liver transplantation, hepatitis C, Child-Pugh class C                   |
| 9       | M      | 50  | 24.7 | Transplant nephrectomy, coronary artery disease                          |
| 10      | M      | 48  | 28.3 | Liver transplantation, liver cell carcinoma, Child-Pugh class C          |

<sup>a</sup>BMI, body mass index; EDD, extended daily dialysis.

Table 2. Demographic of the studied critically ill patients who were treated with levofloxacin and EDD

| Patient | Gender | Age | BMI  | Main Diagnosis  |
|---------|--------|-----|------|---|
| 1       | F      | 33  | 23.9 | Liver transplantation, rhabdomyolysis, Child-Pugh class C |
| 2       | M      | 57  | 22.5 | Diabetic nephropathy, septic shock                        |
| 3       | M      | 58  | 30.1 | Pancreatitis  |
| 4       | M      | 62  | 26.1 | Kidney transplantation, ulcerative colitis                |
| 5       | M      | 50  | 16.9 | Lung transplantation, lung fibrosis                       |

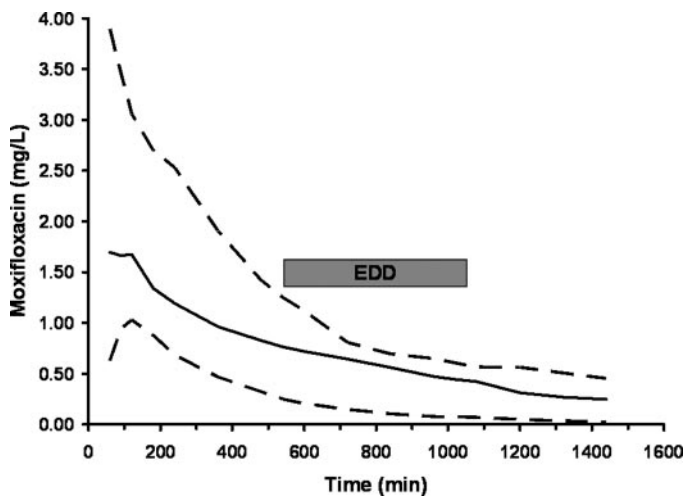


Figure 1. The time concentration curves for moxifloxacin are presented as median (continuous line) and range (broken line).

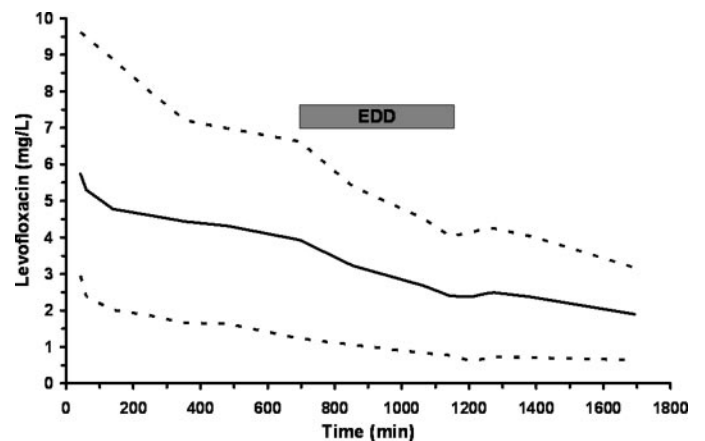


Figure 2. The time concentration curves for levofloxacin are presented as median (continuous line) and range (broken line).

of 2.93 to 3.12 L/h, the half-life of levofloxacin during dialysis was reduced to 10.3 h (range 10.0 to 10.6 h).

These data are summarized and compared with the results reported for IHD and CRRT in the literature in Tables 3 (moxifloxacin) and 4 (levofloxacin). No adverse effects were attributable to the use of moxifloxacin and levofloxacin in our patients.

### Discussion

This study provides the first pharmacokinetic data of moxifloxacin and levofloxacin during EDD. The pharmacokinetic

data that were obtained in this prospective study in critically ill patients who had ARF and were in the ICU document (1) that both antibiotics moxifloxacin and levofloxacin are eliminated by EDD and (2) that a dose adjustment is necessary only in the case of levofloxacin.

#### Rationale for Using Different Methods to Calculate Dialysis Clearance

We applied several methods to estimate the drug clearance by hemodialysis and the fraction of drug removed by hemodialysis because each method has its limitations. Dialysate-based methods (methods 1 and 3) depend on the stability of the drug

Table 3. Pharmacokinetics of moxifloxacin in intensive care patients with ARF undergoing EDD<sup>a</sup>

| Parameter                            | EDD  | IHD                   | CRRT   |
|--------------------------------------|--|-----------------------|--|
| Membrane                             | Polysulfone 1.3 m <sup>2</sup>   | —                     | Polyacrylonitrile 0.9 m <sup>2</sup> (Ref. 23) |
| Q <sub>B</sub> , Q <sub>D</sub> (ml) | 160, 160   | —                     | 150, —   |
| T <sub>1/2off</sub> (h)              | 12.3 (3.7 to 34.0)   | 14.1 ± 1.23 (Ref. 28) |  |
| T <sub>1/2on</sub> (h)               | 6.0 (3.9 to 11.0)  | 11.6 ± 1.57 (Ref. 28) | 9.87 ± 3.26 (Ref. 23)                          |
| V <sub>d</sub> (L)                   | 266 (154 to 514)   |                       | 270 ± 133 (Ref. 23)                            |
| V <sub>d</sub> (L/kg)                | 3.8 (1.9 to 7.1)   |                       |  |
| CL <sub>off</sub> (L/h)              | 15.7 (8.1 to 49.3)   | 10.8 ± 7.6 (Ref. 28)  |  |
| CL <sub>dial</sub> (L/h)             | 2.0 (0.0 to 4.9) <sup>b</sup><br>3.1 (2.6 to 4.3) <sup>c</sup>                     | 5.72 ± 7.6 (Ref. 28)  | 1.63 ± 0.33 (Ref. 23)                          |
| fract <sub>D</sub> (%)               | 8 (0 to 23) <sup>d</sup><br>34 (0 to 60) <sup>e</sup><br>35 (0 to 50) <sup>f</sup> |                       | 9.99 ± 4.25 (Ref. 23)                          |
| A <sub>dial</sub> (mg)               | 7 (0 to 34)  |                       |  |

<sup>a</sup>Data are median (range). Data were compared with data that were obtained for intermittent hemodialysis (IHD) and continuous renal replacement therapy (CRRT) as reported in the literature. A<sub>dial</sub>, total drug amount recovered from the dialysate; ARF, acute renal failure; CL<sub>dial</sub>, dialysis clearance due to the dialysis system; CL<sub>off</sub>, drug clearance off extended dialysis; fract<sub>D</sub>, fraction of the drug in the body removed by one dialysis treatment; T<sub>1/2off</sub> and T<sub>1/2on</sub>, half-life off and on dialysis treatment; V<sub>d</sub>, apparent volume of distribution.

<sup>b</sup>Estimated from the area under the curve (AUC) during EDD and A<sub>dial</sub>.

<sup>c</sup>Estimated from drug concentrations before and after the dialysis membrane.

<sup>d</sup>Estimated from CL<sub>dial</sub> and V<sub>d</sub>.

<sup>e</sup>Estimated from the half-lives off and on EDD.

<sup>f</sup>Estimated by AUC on the basis of method 5.

Table 4. Pharmacokinetics of levofloxacin in intensive care patients with ARF undergoing EDD

| Parameter                            | EDD  | IHD  | CRRT                                   |
|--------------------------------------|--|--|--|
| Membrane                             | Polysulfone 1.3 m <sup>2</sup>   | Cellulose acetate 2.1 m <sup>2</sup> (Ref. 26) | Polyamide 0.7 m <sup>2</sup> (Ref. 27) |
| Q <sub>B</sub> , Q <sub>D</sub> (ml) | 160, 160   | 400, 600 (Ref. 26)                             | 180, —                                 |
| T <sub>1/2off</sub> (h)              | 34.5 (21.2 to 47.7)  | 34.4 (Ref. 26)                                 | —                                      |
| T <sub>1/2on</sub> (h)               | 10.3 (10.0 to 10.6)  | —  | 8.3 (Ref. 27)                          |
| V <sub>d</sub> (L)                   | 114 (74 to 155)  |  |  |
| V <sub>d</sub> (L/kg)                | 1.71 (1.48 to 1.93)  | 1.35 (Ref. 26)                                 | 4.3 (Ref. 27)                          |
| CL <sub>off</sub> (L/h)              | 3.07 (2.96 to 3.17)  | —  | —                                      |
| CL <sub>dial</sub> (L/h)             | 2.93 (1.51 to 4.35) <sup>a</sup><br>3.12 (3.04 to 3.21) <sup>b</sup>                 | 5.06 (Ref. 26)                                 | 1.65 (Ref. 27)                         |
| fract <sub>D</sub> (%)               | 27 (8 to 46) <sup>c</sup><br>22 (14 to 31) <sup>d</sup><br>17 (7 to 27) <sup>e</sup> | 24.4 (Ref. 26)                                 | 56 (Ref. 27)                           |
| A <sub>dial</sub> (mg)               | 91 (12 to 170)   |  |  |

<sup>a</sup>Estimated from the area under the curve (AUC) during EDD and A<sub>dial</sub>.

<sup>b</sup>Estimated from drug concentrations before and after the dialysis membrane.

<sup>c</sup>Estimated from CL<sub>dial</sub> and V<sub>d</sub>.

<sup>d</sup>Estimated from the half-lives off and on EDD.

<sup>e</sup>Estimated by AUC on the basis of method 5.

in the dialysate and the adsorbence of the drug by the dialysis membrane. Methods that use plasma concentrations before and after the dialysis membrane (method 2) provide information on the drug clearance at a given time, but drug clearance can decrease during hemodialysis. In contrast, methods that use only plasma concentrations from the patient (methods 4 and 5) depend on the terminal half-life of the drug. The estimation of

this terminal half-life can be difficult when the drug distribution is not complete before the start of hemodialysis, when there is a concentration rebound after hemodialysis, and when the observation period is limited by the clinical necessity to administer the next dose.

When the various estimates for a drug are consistent with each other, the confidence in the estimate is increased. When

there are differences between estimates, more insight into the pharmacokinetics of a drug is gained by explanation of these differences.

### Moxifloxacin

Moxifloxacin (molecular weight 437.9 Da) undergoes mainly hepatic metabolism and fecal excretion. Its total clearance is approximately 12 L/h, and its half-life is approximately 12 h in healthy subjects. Only 20% of the drug is excreted unchanged by the kidney (20). Plasma protein binding of moxifloxacin is approximately 54% (21). Renal dysfunction has little effect on the pharmacokinetics of moxifloxacin. In renal failure, the moxifloxacin clearance is reduced by only approximately 20%. Therefore, a dose adjustment is not necessary. However, because moxifloxacin does not only undergo glomerular filtration but also tubular reabsorption, drug clearance by EDD, lacking tubular reabsorption, could be higher compared with normal renal function (22).

In our experiments, one third of moxifloxacin (with regard to the amount of drug present in the body at the beginning of EDD) was removed by one EDD in addition to the nonrenal drug clearance. This is indicated by the difference between the half-lives on and off EDD, the dialysis clearance (method 2), and fraction eliminated by dialysis (methods 4 and 5). In contrast to this finding, only a low amount of moxifloxacin was recovered from the dialysate; consequently, calculations that are based on this amount (methods 1 and 3) lead to low values that underestimate drug removal. Reasons for erroneously low dialysate measurements include adsorption of the drug by the dialyzer membrane and instability of the drug in the dialysate fluid.

Our results suggest that moxifloxacin pharmacokinetics in critically ill patients who have ARF and undergo EDD are similar to those from healthy subjects and patients without renal impairment. These data are in agreement with data that were obtained in critically ill patients who were undergoing continuous venovenous hemodiafiltration, in whom Fuhrmann *et al.* (23) showed that no dosage adaptation was required. Because moxifloxacin primarily undergoes hepatic metabolism and fecal excretion, severe liver impairment, which was present in six of the 10 patients, could have influenced the pharmacokinetic measurements. Whereas no dosage adjustment is necessary in patients with mild or moderate hepatic impairment, the pharmacokinetics of moxifloxacin in patients with severe hepatic impairment (Child-Pugh class C) has to our knowledge not been studied adequately. On the basis of theoretical reasoning, hepatic impairment should decrease hepatic clearance but also could decrease plasma protein binding of moxifloxacin and thereby increase its dialysance. We did not see, however, a distinct difference in pharmacokinetics between patients with and without severe liver impairment. Hence, in anuric critically ill patients, with and without liver impairment, who are undergoing EDD, we recommend a standard dosage of moxifloxacin (400 mg intravenously) administered once daily after the dialysis.

### Levofloxacin

Levofloxacin (molecular weight 370 Da), an enantiomer of ofloxacin, is excreted primarily (80 to 86%) unchanged *via* the kidneys (24). Plasma protein binding of levofloxacin ranges between 24 and 38% (25). Its clearance is approximately 9 L/h, and its half-life is approximately 7 h in healthy subjects. In renal failure, levofloxacin clearance is reduced by approximately 75%, and the half-life is prolonged to 35 h. Therefore, dose adjustments are required in individuals with impaired renal function. Patients who were treated with EDD had a shorter half-life than those who were treated with IHD (26). The half-life during the treatment was similar to the one shown for patients who were on CRRT (27).

In our study, 20 to 30% of levofloxacin was removed by one EDD. This is in agreement with previous estimates in IHD (26). The fractional elimination by the renal replacement therapy itself is comparable to the data that were obtained in IHD (26) but significantly lower than for patients on CRRT (27). We could detect a median of 91 mg of levofloxacin in the total collected dialysate after an 8-h extended dialysis, which is in agreement with the estimated dialysis clearances. Because levofloxacin primarily is excreted renally, liver impairment, which was present in one patient, is unlikely to have influenced the pharmacokinetic parameters. Although a final recommendation of a dosing regime on the basis of our data cannot be provided, a dose adjustment still has to be used, despite using this highly efficient method of renal replacement therapy. With regard to the dialysis clearance, levofloxacin should be administered after EDD.

## Conclusion

In future studies, further dosing recommendations for patients who have ARF in the ICU and are treated with novel modes of renal replacement therapy should be developed to avoid excess mortality as a result of underdosing of a potentially life-saving drug.

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## References

1. Naber KG, Well M, Hollauer K, Kirchbauer D, Witte W: In vitro activity of enoxacin versus ciprofloxacin, fleroxacin, lomefloxacin, ofloxacin, pefloxacin, and rifloxacin against uropathogens. *Chemotherapy* 44: 77–84, 1998
2. Kielstein JT, Kretschmer U, Ernst T, Hafer C, Bahr MJ, Haller H, Fliser D: Efficacy and cardiovascular tolerability of extended dialysis in critically ill patients: A randomized controlled study. *Am J Kidney Dis* 43: 342–349, 2004
3. Kumar VA, Craig M, Depner TA, Yeun JY: Extended daily dialysis: A new approach to renal replacement for acute renal failure in the intensive care unit. *Am J Kidney Dis* 36: 294–300, 2000
4. Kumar VA, Yeun JY, Depner TA, Don BR: Extended daily

- dialysis vs. continuous hemodialysis for ICU patients with acute renal failure: A two-year single center report. *Int J Artif Organs* 27: 371–379, 2004
5. Marshall MR, Golper TA, Shaver MJ, Alam MG, Chatoth DK: Sustained low-efficiency dialysis for critically ill patients requiring renal replacement therapy. *Kidney Int* 60: 777–785, 2001
  6. Marshall MR, Ma T, Galler D, Rankin AP, Williams AB: Sustained low-efficiency daily diafiltration (SLEDD-f) for critically ill patients requiring renal replacement therapy: Towards an adequate therapy. *Nephrol Dial Transplant* 19: 877–884, 2004
  7. Van Biesen W, Eloot S, Verleysen A, Glorieux G, Veys N, Vanholder R, Lameire N: Clamping of the dialysate outlet line in the Genius dialysis system does not alter dialysate flow or clearances. *Nephrol Dial Transplant* 21: 1069–1072, 2006
  8. Vanholder R, Van Biesen W, Lameire N: What is the renal replacement method of first choice for intensive care patients? *J Am Soc Nephrol* 12[Suppl 17]: S40–S43, 2001
  9. Mueller BA, Pasko DA, Sowinski KM: Higher renal replacement therapy dose delivery influences on drug therapy. *Artif Organs* 27: 808–814, 2003
  10. Ahern JW, Lai C, Rebeck JA, Possidente CJ, Weidner M: Experience with vancomycin in patients receiving slow low-efficiency dialysis. *Hosp Pharm* 39: 138–143, 2004
  11. Fiaccadori E, Maggiore U, Rotelli C, Giacosa R, Parenti E, Picetti E, Sagripanti S, Manini P, Andreoli R, Cabassi A: Removal of linezolid by conventional intermittent hemodialysis, sustained low-efficiency dialysis, or continuous venovenous hemofiltration in patients with acute renal failure. *Crit Care Med* 32: 2437–2442, 2004
  12. Kielstein JT, Czock D, Schopke T, Hafer C, Bode-Boger SM, Kuse E, Keller F, Fliser D: Pharmacokinetics and total elimination of meropenem and vancomycin in intensive care unit patients undergoing extended daily dialysis. *Crit Care Med* 34: 51–56, 2006
  13. Manley HJ, Bailie GR, McClaran ML, Bender WL: Gentamicin pharmacokinetics during slow daily home hemodialysis. *Kidney Int* 63: 1072–1078, 2003
  14. Fassbinder W: Renaissance of the batch method? *Nephrol Dial Transplant* 13: 3010–3012, 1998
  15. Lonnemann G, Floege J, Kliem V, Brunkhorst R, Koch KM: Extended daily veno-venous high-flux haemodialysis in patients with acute renal failure and multiple organ dysfunction syndrome using a single path batch dialysis system. *Nephrol Dial Transplant* 15: 1189–1193, 2000
  16. Dhondt AW, Vanholder RC, De Smet RV, Claus SA, Waterloos MA, Glorieux GL, Delanghe JR, Lameire NH: Studies on dialysate mixing in the Genius(R) single-pass batch system for hemodialysis therapy. *Kidney Int* 63: 1540–1547, 2003
  17. Stass H, Dalhoff A: Determination of BAY 12–8039, a new 8-methoxyquinolone, in human body fluids by high-performance liquid chromatography with fluorescence detection using on-column focusing. *J Chromatogr B Biomed Sci Appl* 702: 163–174, 1997
  18. Bottcher S, von BH, Hoppe-Tichy T, Benz C, Sonntag HG: An HPLC assay and a microbiological assay to determine levofloxacin in soft tissue, bone, bile and serum. *J Pharm Biomed Anal* 25: 197–203, 2001
  19. Czock D, Rasche FM: New AUC-based method to estimate drug fraction removed by hemodialysis. *Kidney Blood Press Res* 27: 172–176, 2004
  20. Stass H, Kubitz D, Halabi A, Delesen H: Pharmacokinetics of moxifloxacin, a novel 8-methoxy-quinolone, in patients with renal dysfunction. *Br J Clin Pharmacol* 53: 232–237, 2002
  21. Ostergaard C, Sorensen TK, Knudsen JD, Frimodt-Moller N: Evaluation of moxifloxacin, a new 8-methoxyquinolone, for treatment of meningitis caused by a penicillin-resistant pneumococcus in rabbits. *Antimicrob Agents Chemother* 42: 1706–1712, 1998
  22. Stass H, Dalhoff A, Kubitz D, Schuhly U: Pharmacokinetics, safety, and tolerability of ascending single doses of moxifloxacin, a new 8-methoxy quinolone, administered to healthy subjects. *Antimicrob Agents Chemother* 42: 2060–2065, 1998
  23. Fuhrmann V, Schenk P, Jaeger W, Ahmed S, Thalhammer F: Pharmacokinetics of moxifloxacin in patients undergoing continuous venovenous haemodiafiltration. *J Antimicrob Chemother* 54: 780–784, 2004
  24. Stahlmann R, Lode H: Fluoroquinolones in the elderly: Safety considerations. *Drugs Aging* 20: 289–302, 2003
  25. Fish DN, Chow AT: The clinical pharmacokinetics of levofloxacin. *Clin Pharmacokinet* 32: 101–119, 1997
  26. Sowinski KM, Lucksiri A, Kays MB, Scott MK, Mueller BA, Hamburger RJ: Levofloxacin pharmacokinetics in ESRD and removal by the cellulose acetate high performance-210 hemodialyzer. *Am J Kidney Dis* 42: 342–349, 2003
  27. Traunmuller F, Thalhammer-Scherrer R, Locker GJ, Losert H, Schmid R, Staudinger T, Thalhammer F: Single-dose pharmacokinetics of levofloxacin during continuous venovenous haemofiltration in critically ill patients. *J Antimicrob Chemother* 47: 229–231, 2001
  28. Stass HH, Dammer S, Kubitz D, Moeller J, Delesen H, Schaefer R: No Dose Adjustment Is Needed for Patients Undergoing Hemodialysis (HD) Receiving Oral Moxifloxacin [A-1383], presented at the 42nd ICAAC meeting of the American Society for Microbiology; September 27–30, 2002; San Diego, CA