Ofloxacin Pharmacokinetics in Mechanically Ventilated Patients

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The pharmacokinetics of ofloxacin were studied in 12 intensive care patients, 6 of whom were under controlled mechanical ventilation. All patients had a creatinine clearance of >80 ml/min per 1.73 m². They were given 3 mg of ofloxacin per kg of body weight intravenously at a constant flow rate in 30 min twice a day for 7 days. Pharmacokinetic studies were performed on days 1 and 7. Between days 1 and 7, significant increases in the alpha (distribution) and beta (elimination) phase half-lives, the area under the serum concentration-time curve, and peak and trough levels in serum were observed, together with a marked decrease (>50%) in total body clearance. Possible contributing factors for alteration of ofloxacin pharmacokinetics in ventilated patients were patient age, liver dysfunction, drug interaction, and drug accumulation in a deep compartment. This study shows that in intensive care patients the pharmacokinetics of ofloxacin differ from those reported for healthy volunteers.

Critically ill patients with acute pathologic changes have numerous disorders induced by the causal disease and/or concurrent therapy. These subjects usually receive multiple associated treatments whose cumulative effects are not always predictable, especially in terms of drug elimination. As for antibiotics, it has been demonstrated that various pharmacokinetic disorders can occur in intensive care patients during administration of aminoglycosides (1, 12), beta-lactams (1), or a quinolone (11).

Compared with the results obtained with healthy volunteers, these modifications can lead to changes in the method of administration, i.e., dosage and frequency of injections (1, 12). The aim of this study was to evaluate possible modifications in ofloxacin pharmacokinetics administered to intensive care patients compared with normal subjects.

MATERIALS AND METHODS

This open and prospective study included two groups of patients admitted consecutively to an intensive care unit. The first group consisted of six patients without respiratory problems and therefore without mechanical ventilation. The second group included six patients who were on mechanical ventilation for a minimum of 7 days. These six patients remained under controlled ventilation during the whole study. All of the patients had nosocomial infections with organisms susceptible to ofloxacin. They all had a creatinine clearance of >80 ml/min per 1.73 m². Urine was collected over a 24-h period by an indwelling urinary catheter. Urine and serum creatinine were determined by the Jaffé method by using picric acid in alkaline medium. Creatinine clearance was calculated with the formula \( (U \times V)/P \) (10), where \( U \) is urine creatinine, \( V \) is 24-h urine, and \( P \) is serum creatinine. Ofloxacin was given intravenously at a dose of 3 mg/kg, twice daily, for a minimum of 7 days. The drug was administered precisely at a constant flow rate in 30 min with an automatic pump.

Pharmacokinetic studies were performed on days 1 and 7. Arterial blood samples were taken at the end of infusion at 1, 5, and 10 min and 1, 2, 3, 6, 9, and 12 h. The blood samples were centrifuged, and all were stored at −35°C until assay. Ofloxacin levels in serum were measured by high-performance liquid chromatography. A Merck chromatograph was used, coupled with an L 6200 pump, an L 4000 UV detector, a D 2500 integrator, and a C 18 column (Lichro Cart 250-4, catalog no. 15 539, Lichrosorb RP 18). The mobile phase consisted of 1.36 g of K2HPO4 and 40 ml of tetrabutylammonium (0.05 M) in 1 liter of H2O-acetonitrile (85/15). Detection sensitivity was 0.04 µg/ml (12). Coefficients of variation were 1.5% for within-day variation and 2.2% for between-day repeatability assays.

For pharmacokinetic analysis, ofloxacin concentrations in serum were plotted against time and pharmacokinetic parameters were determined with an Apple II E computer by conventional methods (16) with our own software. Curve fitting of the data was done by the method of residuals as described by Wagner (16). The alpha and beta phases were assessed by linear regression (two to four points for the alpha phase and four or five points for the beta phase). In all cases, the two-compartment model was preferred as judged by coefficient-of-correlation and least-squares sums. Since ofloxacin kinetics were determined under real-life conditions, only nine sampling times were chosen. Thus, obviously, a tricompartimental model could not be used. The parameters assessed were alpha and beta phase elimination half-lives \( (t_{1/2\alpha} \text{ and } t_{1/2\beta}) \), area under the serum concentration curve from time zero to 12 h (AUCO–12), extrapolated to infinity (AUCO–∞), total plasma clearance (CL), and central volume of distribution (V). All of these parameters were calculated by using standard formulas (16). Because of the blood sampling schedule, elimination (beta phase) half-life estimation was difficult on day 7 (marked increase in ofloxacin trough levels in serum). Thus, comparisons of AUC between days 1 and 7 were performed by using AUCO–12 instead of AUCO–∞, and calculations of CL and V on day 7 were also performed by using AUCO–12. On day 1, CL and V were calculated by using AUCO–∞.

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The results are presented as means ± standard deviations (SD). Comparisons between the two groups and within the groups were made with the Student t-test for paired and unpaired data. The level of significance was P < 0.05.

RESULTS

All 12 patients received parenteral nutrition (30 cal [1 cal = 4.184 J/kg/day as glucose and lipids and 0.15 to 0.2 g of nitrogen per kg/day) and gastric protection in the form of alkaline solutions (30 ml of Maalox six times per day). In addition, all patients in both groups were given subcutaneous or intravenous heparin for prevention of venous thrombosis. The other drugs received by patients are summarized in Table 1. In the ventilated group, the underlying diseases were multiple trauma (one patient), gastrectomy for cancer (one patient), occlusion (one patient), and AIDS (one patient). Associated diseases in the ventilated group were acute-phase myocardial infarction (one patient), multitrauma (one patient), and coelectomy for cancer (one patient). There were no differences between the two groups at the beginning of the study (day 1) with respect to the parameters presented in Table 2, except for the level of bilirubin. In addition, there were no differences between the two groups in the following parameters: prothrombin time, protidemia, alkaline phosphatase, and serum transaminase. Table 3 presents the evolution of the pharmacokinetic parameters. At the time of inclusion, the two groups did not differ in CL and V. On day 7, there was a significant increase in CL and V. In the ventilated group, peak levels in serum (1 min) increased from 12.6 ± 3.1 mg/liter on day 1 to 20 ± 6 mg/liter on day 7 (P < 0.01) and trough levels (12 h) increased from 1.4 ± 0.05 mg/liter on day 1 to 6.4 ± 4 mg/liter on day 7 (P < 0.02). In the nonventilated group, only trough levels were significantly increased, from 1.1 ± 0.4 mg/liter on day 1 to 3.4 ± 1.5 mg/liter on day 7 (P < 0.05).

DISCUSSION

Pharmacokinetic studies of ofloxacin in healthy subjects after both oral and parenteral administrations have been well documented (2–5, 7–9, 14, 15). The characteristics determined after a single dose are excellent bioavailability (close to 1), a t1/2 of 5 to 7 h, an elevated V (approximately 2 liters/kg), very low metabolism (less than 5% of the dose), rapid elimination almost exclusively through the kidneys in unchanged form, and low binding to plasma proteins (approximately 10%).

During repeated administration of ofloxacin, a low level of drug accumulation (near 1.5) has been noted in some studies (3, 4, 7) but not in others (5, 8). However, these studies were performed for short periods (3 or 4 days) and with healthy volunteers (4, 5, 7, 8). There is no available information on the possible pharmacokinetic modifications of ofloxacin in patients with unstable situations or major modifications in physiological functions. The present study on this type of patient, with a particular interest in subjects on mechanical ventilation, revealed differences from the results obtained with healthy volunteers. On administration of ofloxacin on day 1, there were no differences between the two groups and their pharmacokinetic parameters differed little from those previously reported, except perhaps in slightly lower values for CL and V and slightly higher-than-normal values for AUC (3–8, 13, 14). This can probably be explained by the fact that the present study was performed with relatively old patients (15). On day 7, there were marked increases in AUC, t1/2, t1/2B, and levels in serum. Thus, use of repeated doses of ofloxacin led to marked drug accumulation. This was more pronounced in the group of ventilated patients. This phenomenon was confirmed by the decrease in CL values in the patients under mechanical ventilation. For methodological reasons (see Materials and Methods), AUC0–12 was used instead of AUC0–∞ for calculation of CL on day 7.

In this study, the patients on mechanical ventilation were older than the nonventilated patients. Although the difference in age did not reach the level of significance, we cannot

| TABLE 1. Concurrent therapy administered during the study to patients receiving ofloxacin |
|---------------------------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|
| Patient group                  | Inotropic support | Heparin | Antiarrhythmic agents | Furosemide | Nitroglycerin | Antifungal agent | Total parenteral nutrition |
| (n = 6)                        | (dopamine, dobutamine) | (intravenous or subcutaneous) | (amiodarone, dysoxipryamide, digoxin) |                  |                  | (intravenous) |                      |
| Ventilated                     | 4               | 6     | 5               | 3           | 1     | 1       | 0               | 6               |
| Nonventilated                  | 1               | 6     | 0               | 1           | 0     | 0       | 2               | 6               |

| TABLE 2. Comparisons of ventilated and nonventilated patients on days 1 and 7 |
|---------------------------------|----------------|----------------|----------------|----------------|----------------|----------------|
| Patient group                  | Age (yr) | Wt (kg) | Serum creatinine (µM/liter) on day: | Creatinine clearance (ml/min · 1.73 m²) on day: | Bilirubin (µM/liter) on day: | Albuminemia (µM/liter) on day: |
| (n = 6)                        |          |        | 1    | 7    | 1    | 7 | 1    | 7 | 1    | 7 | 1    | 7 |
| Ventilated                     | 69 ± 6  | 65 ± 10 | 67 ± 20 | 62 ± 12 | 97 ± 24 | 104 ± 30 | 67 ± 40⁴ | 130 ± 70⁴ | 341 ± 65 | 305 ± 98 |
| Nonventilated                  | 59 ± 12 | 67 ± 12 | 85 ± 21 | 81 ± 20 | 100 ± 24 | 86 ± 30 | 13 ± 13 | 13 ± 8 | 345 ± 30 | 349 ± 48 |

⁴ P < 0.001 for the ventilated-nonventilated comparison on days 1 and 7.

⁵ P < 0.005 for the ventilated-nonventilated comparison on day 7.
rule out a type II error because of the small sizes of our two groups. Thus, we may have missed a significant difference in this parameter. Part of our results may be explained by the fact that age is a factor known to alter the pharmacokinetics of ofloxacin (15). However, the phenomenon of drug accumulation was also seen in the group of patients with a lower mean age (nonventilated patients). The role of concurrent therapeutics, given in association with ofloxacin, can also be discussed. More patients in the ventilated group were receiving concomitant therapy (Table 1), probably because of more severe underlying conditions, but none of the drugs used are known to interfere with ofloxacin elimination. The use of magnesium-aluminum hydroxide (Maalox) in each patient deserves special attention, since it would prevent any enterohepatic recycling of ofloxacin because of chelate formation. Although the main route of ofloxacin elimination is through the kidneys in unchanged form, part of the drug is eliminated by nonrenal clearance. The ventilated patients exhibited some biological signs of liver dysfunction (especially a marked increase in bilirubin level). This impairment of liver function could partly explain the perturbation in ofloxacin pharmacokinetics.

Quinolones are antibiotics that can be ion-trapped inside cells. Thus, accumulation in a deep tissue compartment may occur after multiple dosing. The present study was carried out under real-life conditions, and only nine sampling times were scheduled; thus, tricompartmental analysis could obviously not be performed. By using a simpler two-compartment model, we may have missed demonstration of the existence of a deep-tissue compartment. The decrease in CL, as this deep site becomes saturated, may also be explained by the use of a simpler, “incorrect” model.

As renal elimination accounts for most ofloxacin clearance, renal impairment has a major impact on drug disposition (6). In the present study, evaluation of renal function was performed by calculating creatinine clearance. After collection of urine over a 24-h period and measurement of serum and urine creatinine, clearance was calculated by the standard formula (10). The use of formulas or nomograms based on anthropometric parameters and serum creatinine measurement may lead to erroneous estimation of glomerular filtration in intensive care patients (10). Between days 1 and 7, no significant changes in creatinine clearance were observed in the two groups. However, a risk of type II error in the statistical evaluation cannot be ruled out, since small groups of patients were studied. Thus, mild impairment of renal function in the study patients may have been missed. This could also partly explain the phenomenon of ofloxacin accumulation.

Ofloxacin levels in serum increased from days 1 to 7 as a direct consequence of drug accumulation. Since ofloxacin has excellent tolerance, this phenomenon may present a beneficial microbiological aspect in that better efficacy can be achieved against certain organisms for which the MIC is high. If, however, one wishes to maintain serum levels within normal ranges, a reduction in the dose or an increase in the time between injections, beginning on 4 or 5, should probably be considered.

In conclusion, this study shows that in intensive care patients with clinical instability and mechanical ventilation,
the pharmacokinetics of ofloxacin differ from those reported for healthy volunteers. Increases in AUC, $t_{1/2a}$, $t_{1/2b}$, and levels in serum were observed, accompanied by a reduction in CL.

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AUTHOR’S CORRECTIONS

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Long-Term Protection of Polyaspartic Acid in Experimental Gentamicin Nephrotoxicity

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