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Penetration of Ciprofloxacin into Bronchial Secretions from Mechanically Ventilated Patients with Nosocomial Bronchopneumonia

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The aim of the study was to evaluate the penetration of ciprofloxacin into bronchial secretions from mechanically ventilated patients with nosocomial bronchopneumonia. For this purpose, in each patient studied, simultaneous serial blood and bronchial secretion samples were obtained over a 12-h period on days 2 and 4. Eight patients were included in the study. Ciprofloxacin was given at a dose of 200 mg over 30 min by using an automatic pump. Ciprofloxacin was measured by high-performance liquid chromatography. Peak levels of drug in serum were 2.95 ± 1 mg/liter on day 2 and 2.43 ± 0.7 mg/liter on day 4. Peak and trough levels in bronchial secretions were 0.95 ± 0.51 and 0.21 ± 0.12 mg/liter, respectively, on day 2 and 0.76 ± 0.17 and 0.18 ± 0.14 mg/liter, respectively, on day 4. The ratios of peak concentrations in bronchial secretions/serum were 0.32 ± 0.11 and 0.33 ± 0.06 on days 2 and 4, respectively. The ratios of the area under the concentration-time curve from 0 to 12 h (AUC_{0-12}) for bronchial secretions/those for serum were 0.66 ± 0.40 and 0.55 ± 0.30 on days 2 and 4, respectively. A significant positive correlation was found on day 4 between the AUC_{0-12} for serum and the AUC_{0-12} for bronchial secretions. No significant correlations were found between peak values in serum and bronchial secretions.

Ciprofloxacin is a fluoroquinolone with a broad spectrum of activity, including activity against staphylococci and gram-negative bacteria, including most members of the family *Enterobacteriaceae* and *Pseudomonas aeruginosa* (1, 22). Weaker activity against gram-positive cocci other than staphylococci has also been reported. These bacteriological aspects make this antibiotic of interest for the treatment of nosocomial bronchopneumonia (23). Bronchial tree colonization by pathogens coming from the patient's oropharynx and secondary bronchial tree infection are the main pathogenic mechanisms of nosocomial bronchopneumonia acquired by intubated patients under mechanical ventilation (16, 19). Therefore, it is of interest to determine the degree of penetration of ciprofloxacin into bronchial secretions when this drug is used to treat nosocomial pulmonary infections. Penetration of ciprofloxacin has been studied in patients with cystic fibrosis or acute exacerbation of chronic bronchitis (5, 6, 8, 10, 12, 17, 24). No information is available, to our knowledge, on mechanically ventilated patients with nosocomial bacterial bronchopneumonia in intensive care units.

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After institutional approval and informed consent from the families of the patients were obtained, eight patients were included in the study (mean age, 66 ± 17 years; mean weight, 69 ± 14 kg). These patients were under controlled mechanical ventilation and were sedated (phenoperidine, 1 mg/h) and paralyzed (vecuronium, 2 mg/h). They presented with nosocomially acquired pneumonia, and all patients had to fulfill the following diagnostic criteria: purulent sputum; body temperature, ≥38.5°C; leukocyte count, ≥12,000/mm^3; new or progressive infiltrate on chest X ray; hypoxia which required the use of positive end-expiratory pressure or an increase in fraction inspiratory oxygen concentration; no other site of infection; and growth of a pathogenic bacterium on a protected specimen brush or bronchoalveolar lavage specimens. The pathogens that were isolated were *P. aeruginosa* (six patients), *Enterobacter aerogenes* (one patient), and *Klebsiella pneumoniae* (1 patient). Five patients had a mild impairment of their renal function, with a creatinine clearances of between 60 and 70 ml/min/1.74 m^2. The other three patients had creatinine clearances of >80 ml/min/1.74 m^2.

Patients were given 200 mg of ciprofloxacin intravenously once every 12 h over 30 min at a constant flow rate via an automatic pump and a central venous line. They were concomitantly given imipenem or ceftazidime. All patients were receiving total parenteral nutrition (glucose, lipid, nitrogen, and trace elements). No patients were receiving aminophylline or histamine H_2 receptor blockers. The pharmacokinetic analysis was performed on days 2 and 4 of treatment. Blood samples were obtained via an arterial catheter (radial artery) at 10 min, (peak level) and at 1, 2, 4, 6, 8, 10, and 12 h (trough level) after the infusion. Simultaneously, samples of bronchial secretions were obtained via a mucus aspirator (Lukens aspirator 534-16; Vygon, Ecouen, France) through the endotracheal or the tracheostomy tube. Blood samples were immediately centrifuged, and serum samples were stored at −35°C until they were assayed. Bronchial samples were also stored at −35°C. The levels of ciprofloxacin in serum and bronchial secretions were determined by high-performance liquid chromatography (HPLC) (9).

Specimen preparation procedure. For determination of the levels of ciprofloxacin in serum, 50 μl of the sample was mixed

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with 1 ml of phosphate buffer (pH 3.0). After mixing (15 s) and centrifugation 5 min at 3,000 rpm (Sorvall centrifuge), the aqueous phase (20 μl) was injected onto the HPLC system. For determination of ciprofloxacin levels in bronchial secretions, samples were weighed and centrifuged. This yielded a clear supernatant which was treated as described above for the serum samples.

HPLC system. Ciprofloxacin concentrations were determined by using a dual-column HPLC system with UV detection (Hitachi F-1050). The precolumn (LiChrospher RP 18 E, 5 μm, 125 by 4 mm [inner diameter]) was connected to the analytical column (LiChrospher RP 18 E, 5 μm, 125 by 4 mm [inner diameter]). The mobile phases consisted of 7% acetonitrile–93% 0.01 M phosphoric acid and 0.005 M tetrabutylamonium hydroxide buffer (pH 3.0). The flow rate was 1.5 ml/min, and ciprofloxacin was detected by use of a fluorescence monitor (λ_{ex}, 282 nm; λ_{em}, 446 nm). The lower limit of detection was 0.015 μg/ml. Calibration curves were linear between this lower detection limit and 20 mg/liter. For serum samples, the correlation was $A = 2.1 \times C + 0.0$ ($r = 0.9999$), where C is the ciprofloxacin concentration and A is the area under the chromatogram. For bronchial secretions, the correlation was $A = 3.8 \times C + 0.1$ ($r = 0.9999$). Recoveries were 100% ± 5% and 100% ± 12% for serum and tissue samples, respectively.

For serum samples, results of within-day repeatability assays (10 consecutive tests for each concentration) were 4.1, 2.0, 2.6, and 1.9% for concentrations of 1.0, 2.0, 3.0, and 4.0 μg/ml, respectively. Results of between-day (3 days) repeatability assays (10 consecutive tests for each concentration) were 5.0, 3.3, 3.6, and 2.3% for the same concentrations, respectively. For bronchial samples, results of the within-day and between-day repeatability assays were 1.9, 1.9, and 1.8% and 2.1, 2.0, and 2.0% for concentrations of 0.8, 1.6, and 1.8 μg/ml, respectively.

To perform the pharmacokinetic analysis, serum ciprofloxacin levels were plotted against time, and the pharmacokinetic parameters were estimated by compartmental analysis. Individual serum drug concentration data sets were fitted to a two-compartment open model for five sets of data and to a three-compartment open model for three sets of data. No weighting of the data was performed. The elimination (β)-half-life ($t_{1/2\beta}$), apparent volume of distribution (V), total clearance from plasma (CL), area under the serum concentration-time curve from 0 to 12 h (AUC_{0-12}), and the area under the serum concentration-time curve extrapolated to infinity ($AUC_{0-\infty}$) were obtained. The compartmental models were fitted to plasma ciprofloxacin concentration-time data by using a nonlinear least-squares regression program (15). The AUCs were calculated by the log-trapezoidal method (25). CL and V were calculated according to the following equations: $CL = F \times dose/AUC$ (where F is bioavailability [$F = 1$]) and $V = CL/k_{el}$ (where k_{el} is the elimination rate constant).

Evaluation of ciprofloxacin penetration into bronchial secretions was performed as follows. For each patient, ratios of the concentration of ciprofloxacin in bronchial secretions to those in serum serum (B/S ratios) were calculated by using peak serum and bronchial secretion ciprofloxacin concentrations. For individual bronchial secretions, the AUC_{0-12} was obtained by plotting bronchial secretion ciprofloxacin concentrations against time and by using the log-trapezoidal rule (25). Then, for each patient, the ratio of the AUC_{0-12} for bronchial secretions to that for serum (AUCB/AUCS ratio) was calculated.

Results are presented as means ± standard deviations. The statistical analysis was performed by using Student's t test for paired data and a linear regression test. A P value of less than 0.05 was considered significant.

TABLE 1. Pharmacokinetics of ciprofloxacin after intravenous injection of 200 mg (30 min) in eight patients with nosocomially acquired bronchopneumonia under controlled mechanical ventilation[a]

Day	$AUC_{0-\infty}$ (μg · ml^{-1} · h)	V (liters · kg^{-1})	CL (ml · min^{-1} · kg^{-1})	$t_{1/2\beta}$ (h)
2	13.4 ± 6.7 (23.9–6.5)	2.5 ± 1.2 (4.1–1.5)	4.5 ± 1.8 (7.4–1.9)	6.7 ± 2.2 (9.9–4.3)
4	13.9 ± 9.3 (31.5–3.9)	3.7 ± 2.2 (7.9–1.5)	5.7 ± 3.8 (12.3–1.4)	7.9 ± 2.4 (12.2–4.9)

[a] Values are means ± standard deviations. Values in parentheses are ranges. No significant difference was observed between days 2 and 4.

Table 1 provides the values of the pharmacokinetic parameters determined for the patients in intensive care units. The relatively long $t_{1/2}$s that we observed were probably related to the mild impairment in renal function observed in five of the eight patients. There was no significant change between the $t_{1/2}$s determined on days 2 and 4 of the study. Figure 1 provides the serum and bronchial secretion ciprofloxacin concentrations plotted against time on day 4. Similar results (data not shown) were observed on day 2. The penetration of ciprofloxacin into bronchial secretions is described in Table 2. The mean peak levels of drug in sera and bronchial secretions were not modified between days 2 and 4. The maximum bronchial secretion ciprofloxacin level was observed 10 min after the end of infusion in six patients and 30 min after the end of infusion in two patients on both days 2 and 4. The ciprofloxacin penetrations into bronchial secretions estimated from B/S ratios was 0.32 ± 0.10 and 0.33 ± 0.14 on days 2 and 4, respectively (P was not significant) (Table 2). Higher values (day 2, 0.66 ± 0.40; day 4, 0.55 ± 0.30) were obtained when ciprofloxacin diffusion was estimated from AUCB/AUCS ratios (Table 2). On day 2, no correlation was found between peak ciprofloxacin concentrations in bronchial secretions and sera (concentration in bronchial secretions = 0.3 in serum concentration + 0.1; $r = 0.58$; P was not significant) or between AUCB and AUCS (AUCB = 0.37 AUCS + 2.3; $r = 0.32$; P was not significant). On day 4, no correlation was found between peak ciprofloxacin concentrations in bronchial secretions and sera (concentration in bronchial secretions = 0.2 concentration in serum + 0.3; $r = 0.57$; P was not significant), but a positive and significant correlation was found between

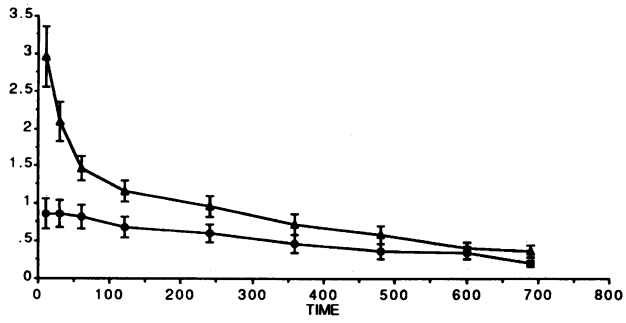

FIG. 1. Ciprofloxacin levels in serum (open triangles) and bronchial secretions (closed circles) plotted against time. Bronchial secretion and serum samples were obtained from each patient at the different sampling times.

TABLE 2. Penetration of ciprofloxacin into bronchial secretions after intravenous injection of 200 mg over 30 in in patients with nosocomially acquired bronchopneumonia under controlled mechanical ventilation

Day	Peak level in serum (10 min (mg · liter^{-1})	Bronchial peak level in bronchial secretions (mg · liter^{-1})	Last determined level in bronchial secretions (690 min) (mg · liter^{-1})	B/S ratio	AUC_{0-12} for bronchial secretions (mg · liter^{-1} · h)	AUCB/AUCS
2	3 ± 1.1 (4.7–1.6)	1 ± 0.5 (2.1–0.5)	0.2 ± 0.1 (0.4–0.0)	0.32 ± 0.1 (0.54–0.14)	5.9 ± 4.4 (15–2.6)	0.66 ± 0.4 (1.3–0.22)
4	2.4 ± 0.7 (3.5–1.6)	0.8 ± 0.2 (1–0.5)	0.2 ± 0.1 (0.4–0.0)	0.33 ± 0.06 (0.44–0.27)	4.2 ± 1.4 (14–2.5)	0.5 ± 0.3 (1.1 ± 0.28)

AUCB and AUCS (AUCB = 0.21 AUCS + 2.2; $r = 0.73$; $P < 0.05$). This suggests that penetration of ciprofloxacin into the bronchial secretions is related to the concentration of ciprofloxacin achieved in serum.

Ciprofloxacin penetration into lung tissues has been studied in patients with cystic fibrosis (8, 10, 11, 17, 20, 24) and in nonventilated patients with acute exacerbation of chronic bronchitis (7, 12). The present study focused on ciprofloxacin penetration into bronchial secretions collected from mechanically ventilated patients in intensive care units with a diagnosis of nosocomially acquired pneumonia. Determination of antibiotic penetration into bronchial secretions is usually based on calculation of the B/S ratio at the time of the maximum concentration of drug in bronchial secretions (4, 14). However, this simple method reflects only the quantity of drug present at a given time. The present study was done by a different approach and compared the AUCs for serum and bronchial secretions. This method provides a more accurate assessment of the bioavailability over the 12-h period between two injections. The penetration of ciprofloxacin was estimated to be between 55 and 66% of the levels in serum by the AUCB/AUCS ratio method, as opposed to only 32% by the B/S ratio method. In the present study, a significant positive correlation was found on day 4 between ciprofloxacin concentrations in sera and bronchial secretions. This suggests that during the steady-state period, higher levels of drug in serum are correlated with higher levels of drug in bronchial secretions. On hour 12, ciprofloxacin levels in bronchial secretions were lower than the MICs for 90% of the main pathogens responsible for nosocomially acquired bacterial pulmonary infections (1, 19). For the treatment of nosocomial infections in patients under mechanical ventilation in intensive care units, it appears advisable to use antibiotic levels greater than or equal to the MICs for 90% of the involved pathogens. By integrating pharmacokinetics, bacterial susceptibility, and bacteriologic response, Peloquin et al. (21) identified the relationship between the antibiotic concentration in vivo and bacterial susceptibility in vitro. If pharmacokinetic studies are performed in a subpopulation such as ventilated patients in an intensive care unit, a specific dosage regimen might be defined to allow for a better clinical response. To achieve this goal, on the basis of the correlation between the AUC for serum and the concentration of drug in bronchial secretions, and given the low level of toxicity of the drug (13), dosages such as 400 or 600 mg given once every 12 h could be considered (2, 3). This is consistent with an in vitro model of *P. aeruginosa* infection in which ciprofloxacin dosages of 200 mg given once every 12 h resulted in bacterial regrowth because of the selection of drug-resistant bacteria (18).

In conclusion, the present study showed that when ciprofloxacin is administered at a dosage of 200 mg twice a day for the treatment of nosocomially acquired bronchopneumonia in patients under mechanical ventilation, penetration of the drug into bronchial secretions is 55 to 60% of the levels of drug in serum. In some patients, bronchial secretion ciprofloxacin levels are lower than the MICs for 90% of most pathogens responsible for nosocomially acquired pulmonary infections. Thus, for the treatment of nosocomially acquired lung infections in compromised patients, ciprofloxacin could be used at a dose of greater than 200 mg or at a rate of three injections per day in order to maintain levels in bronchial secretions greater than or equal to the MICs for 90% of the pathogens throughout the period between two injections.

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