Pharmacokinetics of Piperacillin-Tazobactam in Anuric Intensive Care Patients during Continuous Venovenous Hemodialysis

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The pharmacokinetics of piperacillin-tazobactam were investigated in eight anuric intensive care patients treated by continuous venovenous hemodialysis (CVVHD). The elimination half-life of piperacillin was 4.3 ± 1.2 h, and that of tazobactam was 5.6 ± 1.3 h. The contribution of CVVHD to the overall elimination was relevant (>25%) for both drugs.

Piperacillin-tazobactam is a β-lactam–β-lactamase inhibitor combination with a broad spectrum of antibacterial activity against gram-positive as well as gram-negative pathogens. It is frequently used for the empirical treatment of infection in intensive care patients (2, 15). The aim of this investigation was to determine the pharmacokinetics of piperacillin-tazobactam in critically ill patients with acute anuric renal failure treated by continuous venovenous hemodialysis (CVVHD).

Eight critically ill patients were included in the investigation (Table 1). Inclusion criteria were an age of >18 years, acute renal failure treated by CVVHD, anuria (<100 ml of urine/day), and treatment with piperacillin-tazobactam. Patients with severe liver failure or cholestasis were excluded. The protocol of the study was approved by the local ethical committee, and informed consent was obtained from a first-degree relative. CVVHD was performed with an AN69 hollow-fiber dialyzer (Multiflow 60; Hospal, Nuremberg, Germany) under the following conditions: a blood flow rate of 150 ml/min, a dialysate flow rate of 1.5 liters/h, and an ultrafiltrate flow rate of 80 to 200 ml/h. Doses of piperacillin-tazobactam (4.5 g of Tazobac; Wyeth-Lederle) and dosing schedules were chosen empirically by the attending physicians (Table 2). Piperacillin-tazobactam was administered intravenously over 15 min. Corresponding predialyzer blood samples and dialyzer-outlet dialysate samples were taken before drug administration, at 10 and 30 min after infusion, and at 1, 2, 4, 6, 8, 12, 20, 22, and 24 h after infusion. Sampling was performed in the first dosage interval after the dialyzer membrane was changed. Blood samples were centrifuged immediately after they were taken, and plasma and dialysate samples were frozen at —80°C until analysis. The concentrations of piperacillin and tazobactam were determined by reversed-phase high-performance liquid chromatography with UV detection, with modification of the methods reported previously (13, 16). Plasma specimens were deproteinated, and dialysate was used without pretreatment. The presence of piperacillin was determined from the water layer extracted with dichloromethane; tazobactam samples were derivatized with 1,2,3-triazole and injected without extraction. The chromatographic conditions for piperacillin were as follows: a guarded Superspher C18 100-5/250 μm column, an eluent of methanol-KH2PO4 (1:1, vol/vol; 67 mM; pH 3), ambient temperature, a flow rate of 0.5 ml/min, a λ of 214 nm, and a retention time of ~20 min. The chromatographic conditions for tazobactam were as follows: a Superphys C18 100-5/250 μm column; an eluent of acetonitrile-Na2HPO4 (1:3, vol/vol; 1 mM), Na2HPO4 (1 mM), and tetrabutylammoniumbromide (5 mM) (pH 3); a temperature of 40°C; a flow rate of 0.5 ml/min; a λ of 326 nm; and a retention time of ~6 min. The assay was calibrated over a linear concentration range of 5 to 100 mg/liter and validated at 5, 10, and 100 mg/liter (19). In each matrix (plasma and dialysate), the limit of quantification for both substances was below 1 mg/liter; the intraday and interday coefficients of variation (n = 5) did not exceed 5 and 9% for piperacillin and 4 and 8% for tazobactam, respectively; accuracies were between 97 and 107%.

Concentration time data for piperacillin and tazobactam were analyzed with Topfit 2.0 (5). By nonlinear least-square regression analysis, plasma samples were best fitted to an open one-compartment model. The Akaike information criterion was used for the selection of the model and determination of the best fit. The estimated values from the fitted model were used to derive the volume of distribution (V), the elimination half-life (t1/2), the total body clearance (CLtotal), and rate constants (e.g., the elimination rate constant). The plasma and dialysate areas under the curve (AUCs) were determined from the first to the last data point by the linear trapezoidal method. The CL via CVVHD (CLCVVHD) was calculated by the equation CLCVVHD = (AUCdialysate · dialysate flow rate)/AUCplasma, where AUCdialysate · dialysate flow rate describes the amount of drug eliminated into the dialysate (6, 9, 20). The saturation coefficient (SC) was determined by the equation SC = AUCdialysate/AUCplasma (9). The fraction of the elimination by CVVHD (FCVVHD) was determined by the equation FCVVHD = (CLCVVHD/CLtotal) · 100 (17). With the individual pharmacokinetic parameters obtained, steady-state peak and trough plasma concentrations for a simulated dosage regimen were calculated within the given model. These were used to

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calculate the percentage of time of a dosage interval for which the concentration was greater than the MIC (time above MIC), as described by others (8). NCCLS breakpoints for susceptible (16 mg/liter) and intermediate susceptible (32 to 64 mg/liter) gram-negative bacilli and anaerobes were used as MIC estimates (12). An acceptable exposure of pathogens to drugs is considered to have occurred if the time above MIC exceeds 50% of the dosage interval (8). Since in vitro investigation indicated that the antibacterial activity of piperacillin-tazobactam was lost when the amount of tazobactam fell below a critical concentration (11), and susceptibility testing is usually performed with a critical concentration and susceptibility testing is usually performed with a critical concentration (11), the goal for dosage simulation of tazobactam was to calculate the percentage of time of a dosage interval for which the concentration was greater than the MIC (time above MIC). 

Since in vitro investigations suggest that the antibacterial activity of the combination can be used as long as tazobactam does not exceed its MIC. This variability might be due in part to differences in the variability determined in this investigation are comparable with values reported for intensive care patients undergoing CVVHD or CVVH (7, 21) and renal-failure patients with creatinine CL values of >4 mg/liter for at least as long as the concentration of piperacillin exceeded its MIC.

Pharmacokinetic parameters of piperacillin and tazobactam are presented in Table 2. No drug-related adverse effects were observed. Under the conditions chosen for the performance of CVVH in this investigation, saturation coefficients of 0.87 ± 0.21 for piperacillin and 0.64 ± 0.19 for tazobactam were determined. Only solutes that are not bound to plasma proteins can cross the dialyzer membrane. Therefore, these results agree with predictions that were based on the plasma protein binding level of 20 to 30% reported to occur in healthy individuals (15). For intensive care patients undergoing continuous arteriovenous hemodialysis (CAVHD), a saturation coefficient of 0.7 ± 0.21 (standard deviation) for piperacillin was determined (7). CL<sub>total</sub> varied among the patients investigated and ranged from 26 to 220 ml/min (median, 47 ml/min) for piperacillin and from 22 to 59 ml/min (median, 29.5 ml/min) for tazobactam. This variability might be due in part to differences in V<sub>c</sub>. The patient with the highest CL of piperacillin (220 ml/min) had very low peak plasma concentrations and therefore the highest V<sub>c</sub>. Since piperacillin is hydrophilic and distributes extracellularly (15), this might be an indication of fluid overload in this patient. The estimated values of CL<sub>total</sub> and the variability determined in this investigation are comparable with values reported for intensive care patients undergoing CAVHD or CVVH (7, 21) and renal-failure patients with creatinine CL values of <20 ml/min/1.73 m<sup>2</sup> (4). CL via extracorporeal detoxication systems should be considered relevant for dosing if it exceeds more than 25% of CL<sub>total</sub> (17). In this study, the CL<sub>cvvhd</sub> of piperacillin was 37% (median, with a range of 13 to 100%) and the CL<sub>cvvhd</sub> of tazobactam was 38% (median, with a range of 32 to 92%) of CL<sub>total</sub>. Therefore, a relevant contribution of CVVH to the overall elimination of both drugs has to be taken into account. For drug dosage design, V<sub>c</sub> obtained in this investigation are in accordance with the estimated values for CVVH and CAVHD patients (7, 21). As observed for patients with different degrees of renal impairment (2, 3, 15) and for patients undergoing CVVH (21), the t<sub>1/2b</sub> of tazobactam was greater than that of piperacillin, indicating that a relative accumulation of tazobactam may occur. Since in vitro investigations suggest that the antibacterial activity of piperacillin and tazobactam in combination is more dependent on the pharmacokinetics of the inhibitor (tazobactam) and that the antibacterial activity of the combination appeared to be lost when the amount of inhibitor fell below a certain concentration (11), an increase in the elimination of tazobactam over the elimination of piperacillin would require additional doses of tazobactam to the fixed, commercially available combination to retain pharmacodynamic efficacy. With a relative accumulation of tazobactam, as observed in this investigation as well as in cases of renal failure (4, 15), a fixed combination can be used as long as tazobactam does not accumulate to toxic levels. Both piperacillin and tazobactam are considered drugs of low toxicity (18); thus, underestimation of the dosage needs of the critically ill patients is of concern. For each patient, simulations of different dosage regimens (multiple-dose) have been performed by using the individual patient pharmacokinetic data in order to evaluate whether this may help to guide dosage. Simulations of 4,000 mg of piperacillin

<table>
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<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age (yr)</th>
<th>Body wt (kg)</th>
<th>Diagnoses</th>
<th>Urine production (ml/day)</th>
<th>Serum creatinine concn (μmol/liter)</th>
<th>C-reactive protein concn (mg/liter)</th>
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<td>1</td>
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<td>68</td>
<td>100</td>
<td>Renal cell carcinoma, nephrectomy, pneumonia</td>
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<td>62</td>
<td>Emphysema, bronchitis, sepsis</td>
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<td>363</td>
<td>52</td>
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</table>

* F, female; M, male.

<sup>a</sup> Mean age ± standard deviation, 66 ± 9 years.

<sup>b</sup> Mean body weight ± standard deviation, 67 ± 21 kg.
and 500 mg of tazobactam administered every 12 h and 2,000 mg of piperacillin and 250 mg of tazobactam administered every 8 h resulted in times above MIC of >50% for piperacillin with susceptible (MIC of piperacillin = 16 mg/liter; time above MIC, 48 to 100%) and intermediate susceptible (MIC = 32 mg/liter; time above MIC, 17 to 100%) pathogens in seven of eight patients, while the time above 4 mg/liter for tazobactam was 100% for all patients. The patient with the highest \( V \) seemed to fail this dosage regimen and seems to require a higher dosage. Patients with residual renal function and patients that receive continuous renal replacement therapy with higher dialysate flow rates or higher additional hemofiltrate flow rates might have higher (extracorporeal) CL of piperacillin-tazobactam, resulting in higher dosage needs. If available, drug monitoring should be used to individualize treatment with piperacillin-tazobactam for critically ill patients undergoing continuous renal replacement therapy.

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## REFERENCES


