ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, May 2002, p. 1557–1560 Vol. 46, No. 5
0066-4804/02/$04.00+0 DOI: 10.1128/AAC.46.5.1557–1560.2002

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

Silke C. Mueller,[1]* Jolanta Majcher-Peszynska,[1] Heiko Hickstein,[2] Astrid Francke,[3] Annette Pertschy,[4] Martin Schulz,[2] Ralf Mundkowski,[1] and Bernd Drewelow[1]

Department of Clinical Pharmacology, Institute of Experimental and Clinical Pharmacology and Toxicology,[1] Clinic for Internal Medicine,[2] Clinic for Anesthesiology and Intensive Care Medicine,[3] and Clinic for Surgery,[4] University of Rostock, D-18057 Rostock, Germany

Received 16 January 2001/Returned for modification 15 July 2001/Accepted 25 January 2002

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 Nucleosil C_{18} 100-5/250 × 4 column, an eluent of methanol-KH_2PO_4 (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 Superspher C_{18} 100-5/250 × 4 column; an eluent of acetonitrile-Na_2HPO_4 (1:3, vol/vol; 1 mM), NaH_2PO_4 (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 ($t_{1/2\beta}$), the total body clearance (CL_{total}), 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 (CL_{CVVHD}) was calculated by the equation $CL_{CVVHD} = (AUC_{dialysate} \cdot \text{dialysate flow rate})/AUC_{plasma}$, where $AUC_{dialysate} \cdot$ dialysate flow rate describes the amount of drug eliminated into the dialysate (6, 9, 20). The saturation coefficient (SC) was determined by the equation $SC = AUC_{dialysate}/AUC_{plasma}$ (9). The fraction of the elimination by CVVHD (F_{CVVHD}) was determined by the equation $F_{CVVHD} = (CL_{CVVHD}/CL_{total}) \cdot 100$ (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

* Corresponding author. Mailing address: Institute of Experimental and Clinical Pharmacology and Toxicology, Department of Clinical Pharmacology, University of Rostock, Schillingallee 70, D-18057 Rostock, Germany. Phone: 49-381-494-5959. Fax: 49-381-494-5782. E-mail: silke.mueller@med.uni-rostock.de.

TABLE 1. Clinical characteristics of patients participating in the study

Patient	Sex[a]	Age (yr)[b]	Body wt (kg)[c]	Diagnoses	Urine production (ml/day)	Serum creatinine concn (μmol/liter)	C-reactive protein concn (mg/liter)
1	M	68	100	Renal cell carcinoma, nephrectomy, pneumonia	0	539	228
2	F	66	70	Non-Hodgkin's lymphoma, pneumonia	0	150	210
3	M	74	41	Rectal carcinoma, pneumonia	0	300	208
4	M	75	45	Rectal carcinoma, pneumonia	0	142	248
5	M	68	96	Aortocoronary bypass, pneumonia	45	302	302
6	M	44	60	Fibriohistiocytoma, pneumonia	0	253	235
7	F	67	62	Non-Hodgkin's lymphoma, pneumonia	24	131	138
8	M	65	62	Emphysema, bronchitis, sepsis	65	363	52

[a] F, female; M, male.
[b] Mean age ± standard deviation, 66 ± 9 years.
[c] Mean body weight ± standard deviation, 67 ± 21 kg.

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 fixed concentration of 4 mg of tazobactam/liter (12), the goal for dosage simulation of tazobactam was to ensure that the concentration of tazobactam would be >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 CVVHD 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_{total} 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*. The patient with the highest CL of piperacillin (220 ml/min) had very low peak plasma concentrations and therefore the highest *V*. Since piperacillin is hydrophilic and distributes extracellularly (15), this might be an indication of fluid overload in this patient. The estimated values of CL_{total} 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^2 (4). CL via extracorporeal detoxication systems should be considered relevant for dosing if it exceeds more than 25% of CL_{total} (17). In this study, the CL_{CVVHD} of piperacillin was 37% (median, with a range of 13 to 100%) and the CL_{CVVHD} of tazobactam was 38% (median, with a range of 32 to 92%) of CL_{total}. Therefore, a relevant contribution of CVVHD to the overall elimination of both drugs has to be taken into account. For drug dosage design, *V* and $t_{1/2\beta}$ in particular have to be considered. *V* may change during renal insufficiency due to fluid overload, since piperacillin and tazobactam are hydrophilic drugs (10, 15), and it may also vary among the individual patients. As predicted, the estimated *V*'s for the patients investigated are greater than those of healthy subjects (1, 14). The $t_{1/2\beta}$s of both drugs were determined to be fourfold greater than those of healthy subjects (1, 4, 14) and twofold greater than those of subjects with creatinine CL values of <20 ml/min/1.73 m^2 (4). On the other hand, the $t_{1/2\beta}$s 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 $t_{1/2\beta}$ 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

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.

TABLE 2. Pharmacokinetic parameters of piperacillin and tazobactam[a] for eight anuric patients treated by CVVHD

Patient	Dose (g)	Interval (h)	k_{el}[b] (liters/h)	$t_{1/2\beta}$ (h)	*V* (liters/kg)	CL_{total} (ml/min)	CL_{CVVHD} (ml/min)	F_{CVVHD} (%)	SC
1	4, 0.5	12	0.172, 0.120	4.0, 5.8	0.27, 0.11	75, 22	25, 20	33, 92	0.94, 0.77
2	4, 0.5	24	0.159, 0.087	4.4, 7.9	0.25, 0.26	48, 27	20, 9	42, 33	0.80, 0.32
3	2, 0.25	8	0.173, 0.21	4.0, 5.6	0.22, 0.18	26, 26	27, ND[c]	100, ND	1.07, ND
4	2, 0.25	8	0.193, 0.193	3.6, 3.6	0.27, 0.24	44, 32	26, ND	59, ND	1.02, ND
5	4, 0.5	12	0.283, 0.124	2.5, 5.6	0.45, 0.29	220, 58	28, 23	13, 39	1.03, 0.82
6	4, 0.5	12	0.122, 0.128	5.7, 5.4	0.34, 0.41	42, 53	13, 19	31, 37	0.48, 0.69
7	4, 0.5	8	0.136, 0.215	6.2, 6.5	0.33, 0.26	46, 59	19, 19	41, 32	0.69, 0.69
8	4, 0.5	12	0.193, 0.173	3.6, 4.0	0.35, 0.15	72, 26	19, 13	26, 52	0.69, 0.48
Mean ± SD			0.179 ± 0.049, 0.156 ± 0.048	4.3 ± 1.2, 5.6 ± 1.3	0.31 ± 0.07, 0.24 ± 0.09		22 ± 5, 17 ± 5		0.84 ± 0.21, 0.64 ± 0.19
Median (range)						47 (26–220), 29.5 (22–59)		37 (13–100), 38 (32–92)	

[a] Values separated by a comma indicate those for piperacillin and tazobactam, respectively.
[b] k_{el}, elimination rate constant.
[c] ND, not determined.

This work was supported by the Ministry of Education and Research of the Federal Republic of Germany (grant 01EC9404).

We thank K. Kroesche for her skillful technical assistance. Furthermore, we thank the intensive care unit staff for their support.

REFERENCES

1. **Auclair, B., and M. P. Ducharme.** 1999. Piperacillin and tazobactam exhibit linear pharmacokinetics after multiple standard clinical doses. Antimicrob. Agents Chemother. **43:**1465–1468.
2. **Daniel, K. P., and L. C. Krop.** 1996. Piperacillin-tazobactam: a new β-lactam-β-lactamase inhibitor combination. Pharmacotherapy **16:**149–162.
3. **Derendorf, H., and T. Dalla Costa.** 1996. Pharmacokinetics of piperacillin, tazobactam and its metabolite in renal impairment. Int. J. Clin. Pharmacol. Ther. **34:**482–488.
4. **Halsstensen, C. E., M. O. Wong, C. A. Johnson, S. W. Zimmerman, J. J. Onorato, W. F. Keane, M. Doepner, L. Sia, K. Tantillo, S. Bansal, O. Kuye, A. Yacobi, R. Faulkner, and C. D. Lathia.** 1994. Pharmacokinetics of tazobactam M1 metabolite after administration of piperacillin/tazobactam in subjects with renal impairment. J. Clin. Pharmacol. **34:**1208–1217.
5. **Heinzel, G., R. Woloszczak, and P. Thomann.** 1993. Topfit 2.0: pharmacokinetic and pharmacodynamic data analysis system for PC. Gustav Fischer Verlag, Stuttgart, Germany.
6. **Joy, M. S., G. R. Matzke, D. K. Armstrong, M. A. Marx, and B. J. Zarowitz.** 1998. A primer on continuous renal replacement therapy for critically ill patients. Ann. Pharmacother. **32:**362–375.
7. **Keller, E., J. Böhler, A. Busse-Grawitz, P. Reetze-Bonorden, B. Krumme, and P. Schollmeyer.** 1995. Single dose kinetics of piperacillin during continuous arteriovenous hemodialysis in intensive care patients. Clin. Nephrol. **43**(Suppl.)**:**S20-S22.
8. **Kim, M.-K., D. Xuan, R. Quintiliani, C. H. Nightingale, and D. P. Nicolau.** 2001. Pharmacokinetic and pharmacodynamic profile of high dose extended interval piperacillin-tazobactam. J. Antimicrob. Chemother. **48:**259–267.
9. **Krueger, W. A., T. H. Schroeder, M. Hutchison, E. Hoffmann, H.-J. Dieterich, A. Heininger, C. Erley, A. Wehrle, and K. Unertl.** 1998. Pharmacokinetics of meropenem in critically ill patients with acute renal failure treated by continuous hemodiafiltration. Antimicrob. Agents Chemother. **42:**2421–2424.
10. **Lam, Y. W. F., S. Banerji, C. Hatfield, and R. L. Talbert.** 1997. Principles of drug administration in renal insufficiency. Clin. Pharmacokinet. **32:**30–57.
11. **Lister, P. D., A. M. Prevan, and C. C. Sanders.** 1997. Importance of β-lactamase inhibitor pharmacokinetics in the pharmacodynamics of inhibitor-drug combinations: studies with piperacillin-tazobactam and piperacillin-sulbactam. Antimicrob. Agents Chemother. **41:**721–727.
12. **National Committee for Clinical Laboratory Standards.** 2000. Performance standards for antimicrobial disk susceptibility tests, 7th ed. Approved standard M2-A7. National Committee for Clinical Laboratory Standards, Wayne, Pa.
13. **Ocampo, A. P., K. D. Hoyt, N. Wadgaonkar, A. H. Carver, and C. V. Puglisi.** 1989. Determination of tazobactam and piperacillin in human plasma, serum, bile and urine by gradient elution reversed-phase high-performance liquid chromatography. J. Chromatogr. **496:**167–179.
14. **Occhipinti, D. J., S. L. Pendland, L. L. Schoonover, E. B. Rypins, L. H. Danzinger, and K. A. Rodvold.** 1997. Pharmacokinetics and pharmacodynamics of two multiple-dose piperacillin-tazobactam regimens. Antimicrob. Agents Chemother. **41:**2511–2517.
15. **Perry, C. M., and A. Markham.** 1999. Piperacillin/tazobactam: an updated review of its use in the treatment of bacterial infections. Drugs **57:**805–843.
16. **Peyrin, E., Y. Guillaume, and C. Guinchard.** 1995. High-performance liquid

chromatographic determination of tazobactam by precolumn derivatization. J. Chromatogr. B **672:**160–164.
17. **Reetze-Bonorden, P., J. Böhler, and E. Keller.** 1993. Drug dosage in patients during continuous renal replacement therapy. Pharmacokinetic and therapeutic considerations. Clin. Pharmacokinet. **24:**362–379.
18. **Sanders, W. E., and C. C. Sanders.** 1996. Piperacillin/tazobactam: a critical review of the evolving clinical literature. Clin. Infect. Dis. **22:**107–123.
19. **Shah, V. P., K. K. Midha, S. Dighe, I. J. McGilveray, J. P. Skelly, A. Yacobi, T. Layloff, C. T. Viswanathan, C. E. Cook, and R. D. McDowall.** 1991. Analytical methods validation: bioavailability, bioequivalence and pharmacokinetic studies. Conference report. Eur. J. Drug Metab. Pharmacokinet. **16:**249–255.
20. **Tegeder, I., F. Neumann, F. Bremer, K. Brune, J. Lötsch, and G. Geisslinger.** 1999. Pharmacokinetics of meropenem in critically ill patients with acute renal failure undergoing continuous venovenous hemofiltration. Clin. Pharmacol. Ther. **65:**50–57.
21. **Van der Werf, T. S., P. O. M. Mulder, J. G. Zijlstra, D. R. A. Uges, and C. A. Stegeman.** 1997. Pharmacokinetics of piperacillin and tazobactam in critically ill patients with renal failure treated with continuous veno-venous hemofiltration (CVVH). Intensive Care Med. **23:**873–877.