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Pharmacokinetics of piperacillin and tazobactam in critically ill patients with renal failure, treated with continuous veno-venous hemofiltration (CVVH)

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Abstract *Objective:* Kinetics of piperacillin (pip), in combination with the beta-lactamase inhibitor tazobactam (taz) have been studied in volunteers and patients in relatively stable conditions. The fixed drug preparation appeared to have ideal pharmacokinetic properties if renal function was normal or slightly impaired, but no data are available for critically ill patients in anuric renal failure. This study should provide such data.
Patients, design: We studied the pharmacokinetics in nine patients with multiple organ failure, including anuric renal failure, treated with continuous veno-venous hemofiltration (CVVH). Patients received a standard schedule of 4 g pip and 0.5 g taz administered over 0.5 h intravenously, 8 hourly. During 2 consecutive days, the serum levels of both compounds were determined, and total clearance (CI_T) was calculated from serum concentrations.
Results: All nine patients completed day 1, and 8 completed day 2 of the protocol. On day 1, single-dose kinetics showed considerable spread, but pip/taz serum levels followed the pattern as expected, with a pip/taz concentration ratio of 20 : 1. On day 2, however, taz serum concentrations showed a relative increase as compared to pip, resulting in a change in the serum pip/taz concentration ratio to 10 : 1 on day 2. The CI_T of pip was 2.52 ± 1.38 l/h ($t^1/_2$: 5.9 ± 2.9 h), and CI_T of taz 4.44 ± 2.28 l/h ($t^1/_2$: 8.1 ± 3.7 h). The CI_T and $t^1/_2$ of pip and taz correlated highly significantly with clearance by CVVH. Despite a higher CI_T, taz has a longer half-life, because of a higher volume of distribution.
Conclusion: In CVVH dependent patients, pip/taz fixed drug preparations can be used initially, but the pip dosage should be increased relative to that of taz (or interval-adjusted) to prevent cumulation of taz, as compared to the active antimicrobial agent pip.

Key words Piperacillin/tazobactam · Pharmacokinetics · Renal failure · Multiple organ failure · Continuous veno-venous hemofiltration

Introduction

Of all treatment modalities used in the intensive care of patients suffering from sepsis and multiple organ failure, antibiotics are still the cornerstone of management. Nosocomial infections have become leading causes of morbidity and mortality. Pseudomonas aeruginosa, Staphylococcus aureus, Acinetobacter spp., coagulase-negative Staphylococcus (CNS), Bacteroides fragilis and Enterobacteriaceae are important pathogens in these patients, and the associated mortality is high. Piperacillin (pip) is one of the few antimicrobial agents with anti-pseudomonas action available in this setting, but drug susceptibility has become a point of concern.

The combination of pip with tazobactam (taz) has the potential to overcome beta-lactamase mediated antimicrobial resistance.

Plasmid bound beta-lactamases produced by one particular micro-organism may spread drug resistance to other micro-organisms, resulting in a loss of in vivo drug susceptibility. In one large French study in nosocomially infected patients, a reversal of drug susceptibility was achieved if taz was added to pip alone in 89% of clinical isolates [1]. Two Scandinavian phase II studies with data analysis on intention-to-treat basis, comparing the pip/taz combination 4.0/0.5 g t.i.d. with the imipenem/cilastatin 0.5/0.5 g t.i.d. combination in surgical patients with intra-abdominal infections have demonstrated the effectiveness and safety of pip/taz, with either equal [2] or even better cure rates [3]. In a multicentre randomized prospective phase III study from the USA and Canada, comparing pip/taz 3000 mg/375 mg t.i.d. with clindamycin/gentamicin 600 mg t.i.d./2.5–5 mg/kg per day in abdominal infections, pip/taz-treated patients had better clinical and bacteriological responses than the clindamycin/gentamicin-treated patients [4].

In these three studies on clinical and bacteriological effects, however, renal failure and sepsis were an exclusion criterion. In moderate to severe renal failure, the elimination of taz is slightly more affected than pip [5], but the elimination in patients with anuric renal failure treated with continuous veno-venous hemofiltration (CVVH) has not been studied. Furthermore, it can be anticipated that the apparent volumes of distribution may vary with varying degrees of capillary leakage in critically ill patients.

Pharmacokinetic studies in patients treated with CVVH are scarce [6], and most studies on drug elimination in continuous forms of renal replacement therapy have been carried out in continuous arterio-venous hemofiltration. Clearance using CVVH may reach 25–50 ml/min, but on-going clotting within the filter may result in impaired clearance, and several hours may lapse before blocked filters have been changed, with subsequent impaired drug elimination. The elimination of drugs depends primarily on the size of the pores in the filter used and the molecular size, but adsorption to the filter (or to proteins adhering to the filter membrane) may also influence drug elimination. The physico-chemical properties (water-solubility, protein-binding and molecular size) of the two components of the compound drug pip/taz are highly comparable [5], and it is anticipated that the elimination kinetics during CVVH will be similar. Though pip and taz are almost completely excreted in the urine, non-renal clearance may become important in anuric failure and drug metabolism may vary with varying degrees of liver damage. Data on extrarenal clearance in patients with renal failure treated with CVVH of the drugs studied in this protocol are scarce in the literature, and are not available in patients with multiple organ failure and sepsis. The safety profile of pip/taz has been shown to be excellent when compared to many other antibiotic regimens [7]. If, however, the excretion of the two components are different during CVVH, accumulation of one of the components might occur with a possible loss of effectiveness or toxicity.

Patients and methods

Patients aged over 18 years with anuric renal failure, requiring CVVH and in need of antimicrobial treatment including the covering of gram-negative pathogens, as judged by the attending physician, were selected by the investigators among patients admitted to our Intensive Care Unit (ICU) with the consent of the responsible physician. Patients entered the study protocol only after informed, written consent from the patient or his/her first degree relative, spouse or partner, had been obtained. Patients were not eligible if there was any evidence for contraindication, e.g., idiosyncrasy, allergy or other intolerance for the study medication or any other beta-lactam antibiotic agent. This study protocol was approved by the Medical Ethical Committee of the hospital.

The results of a complete physical examination with measurement of body weight, routine laboratory testing, including a complete blood count, blood chemistries, 12-lead ECG, chest radiograph and arterial blood gas analysis with notification of supplemental oxygen or ventilator treatment, were all recorded in the study log, as well as the Acute Physiology And Chronic Health Evaluation (APACHE) II score [7].

Patients received a standard course of pip 4 g and taz 0.5 g intravenously 8 hourly, administered over 0.5 h, after CVVH had been started. Blood samples of 4 mls were collected from an indwelling arterial cannula at 30 min, 1 h, 1.5 h, 2 h, 3 h, 4 h, 6 h and 8 h after administration of the compound drug. After clotting at room temperature, the blood specimen was centrifuged for 10 min at 5000 rpm, and the serum was then stored at –20 °C. On the second day, the blood sampling was repeated in a fashion similar to day 1. After 32 h, when the collection of specimens was completed, the 16 blood samples of each patient were stored at –80 °C and processed and analysed in batches for the determination of taz and pip using High Performance Liquid Chromatography (HPLC) at the hospital Pharmacy Department. Serum 0.2 ml, 0.1 ml methanol, 0.2 ml internal standard (100 μg sulphaquinoxaline/l or phosphate buffer 0.05 M, pH 7.4) and 1 ml of acetonitrile were mixed for 30 s and centrifuged for 5 min. One millilitre of clear supernatant was mixed with 0.75 ml of acetonitrile and 2 ml of dichloromethane. After mixing and centrifugation 15 μl of the supernatant was injected into a HPLC with diode array detection. Gradient mobile phase (from 100% phosphate buffer 0.01 M, pH 2.7 to 50% with acetonitrile in 39 min) was used. The detection limit was less than 1 mg/l both for taz and pip, and coefficient of variation 5.6% for taz and 3.8% for pip. The calibration curves were linear from 1 to 20 mg/l for taz and 1 to 200 mg/l for pip. Additional medical data were collected from patients during their stay in the ICU and the clinical outcome was recorded.

The ultrafiltration rate of the CVVH procedure, which was usually carried out with predilution, was measured over the 8 h of the pharmacokinetic studies. Pharmacokinetic parameter values were calculated by fitting the serum drug concentration data to a two-compartment model by using weighted non-linear least-square regression analysis (KINFIT, MediWare Groningen, the Netherlands) [9]. Correlation between total drug clearance (CI_T),

Table 1 Main patient characteristics (*BW* body weight, *COPD* chronic obstructive pulmonary disease, *DOPA* dopamine, *NOR* norepinephrine, *OLT* orthotopic liver transplantation, *ATN* acute tubulus necrosis, *UTI* urinary tract infection, *RTI* respiratory tract infection, *DIC* diffuse intravascular coagulation, *MV* mechanical ventilation, *CPPV* continuous positive pressure ventilation, *MOF* multiple organ failure, *PBC* primary biliary cirrhosis, *MI* mitral regurgitation, *NIDDM* non-insulin dependent diabetes mellitus, *CPR* cardiopulmonary resuscitation)

No.	age	gender	BW	Diagnoses	APS II	Organs and systems failing	Outcome
1	78	M	85 kg	COPD, ruptured aortic aneurysm, postoperative bleeding, sepsis after relaparotomy, ATN	28	Kidney (ATN), lung (CPPV), circulation (DOPA), DIC	Survived
2	54	F	70 kg	Hepatitis B and C with cirrhosis, chronic renal failure consed by recurrent UTI, sepsis, skeletal tuberculosis	29	Kidney, liver, lung (CPPV), circulation (DOPA, NOR)	Survived
3	48	F	80 kg	Polycythemia vera, Budd-Chiari syndrome with portal hypertension and end-stage hepatic failure with hepato-renal syndrome	34	Liver, kidney, clotting, encephalopathy, circulation (NOR, DOPA)	Survived after OLT
4	49	F	130 kg	Obesity, NIDDM, renal carcinoma, postop. bleeding, relaparotomy, pleural bleeding	26	Kidney (ATN), lung (postoperative MV)	Survived
5	31	M	70 kg	Schizophrenia, epilepsy after brain contusion, alcoholism, intoxication, hypothermia with ATN	31	Kidney (ATN), circulation	Survived
6	77	M	80 kg	COPD, pneumococcal pneumonia, CPR, sepsis with ATN	39	Lung (CPPV), kidney (ATN), circulation	Survived
7	50	M	120 kg	Astrocytoma, low grade, epilepsy, aspiration, sepsis, MOF	30	Lung, kidney (ATN), DIC, circulation (NOR, DOPA)	Died
8	53	F	74 kg	PBC, hepatic failure, hepatorenal syndrome, MI, possible pancreatitis, brain edema	26	Liver, kidney, circulation (NOR), DIC	Died
9	68	M	70 kg	COPD, NIDDM, old myocardial infarction, radiotherapy for prostate carcinoma, digoxin-induced arrhythmia, RTI, CPR, ATN	28	Lung (CPPV), kidney (ATN), circulation	Survived

as calculated by the fitted two-compartment model, and the CVVH ultrafiltration rate was tested by non-parametric Spearman rank correlation.

Results

Nine patients entered the study protocol. The measurements of the blood samples on day 2 in one patient (patient 1, see Table 1) failed, and this patient was therefore excluded from analysis for day 2, so that eight patients were evaluable for analysis. Table 1 shows the main characteristics of the nine patients studied.

Figures 1 and 2 show the mean (SD) serum concentrations of pip and taz on days 1 and 2 of the eight patients studied. On day 1, the serum concentration ratio equalled 20 : 1 while, on day 2, taz concentrations were raised compared to those of pip, resulting in an increase in serum concentration ratio (10 : 1). Pharmacokinetic values were obtained using the MW/PHARM software package for data analysis using a two-compartment model [9]. The $t^1/_2$ of taz was longer than that of pip (see Table 2), despite a higher calculated CI_T of taz, as compared to pip. The calculated CI_T of both taz and pip correlated with the CVVH ultrafiltration rate ($r = 0.63$, $p = 0.02$, and $r = 0.83$, $p < 0.001$, respectively). Calculated CI_T of both taz (74 ± 38 ml/min) and pip (42 ± 23 ml/min) were higher than the CVVH ultrafiltration rate (25.9 ± 9.8 ml/min).

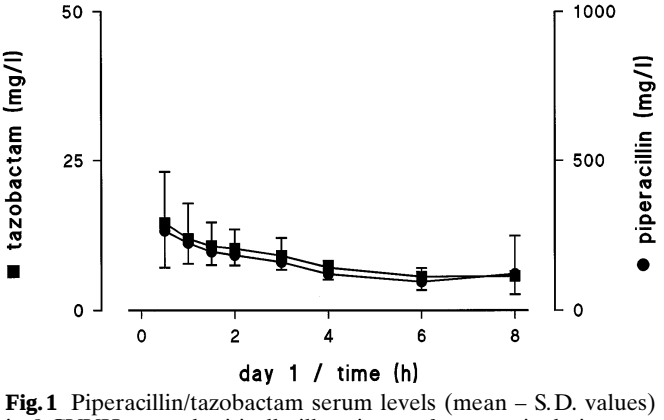

Fig. 1 Piperacillin/tazobactam serum levels (mean – S.D. values) in 9 CVVH-treated critically ill patients, after one single intravenous dose (infusion time 0.5 h) of 4 g pip and 0.5 g taz. Comparative drug levels of the two compounds are 1 : 20. Note different Y-axis for pip *(right)* and taz *(left)*

The microbiological data of the patients were studied. As can be seen from Table 3, no micro-organisms resistant to pip/taz were recovered from our patients in

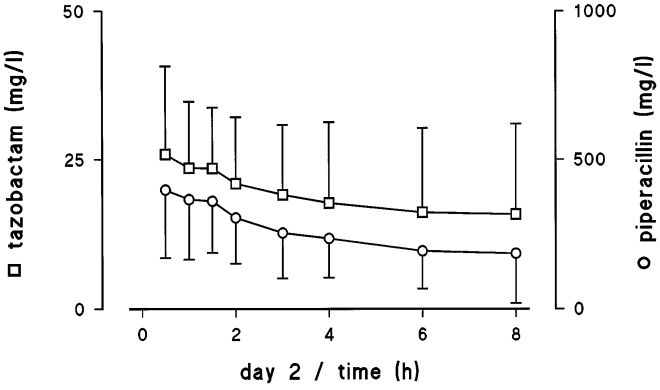

Fig. 2 Piperacillin/tazobactam serum levels (mean – S.D. values) in 8 CVVH-treated critically ill patients, day 2; after 4th intravenous dose (infusion time 0.5 h, 8 hourly) of 4 g pip and 0.5 g taz. Comparative drug levels of the two compounds vary widely but average 1 : 10. Note different Y-axis for pip and taz

the study period, except for yeast and coagulase-negative Staphylococcus (CNS), and although the serum levels of pip/taz varied widely between patients, they were well above the minimal inhibitory levels.

Discussion

Most studies on the pharmacokinetics of antimicrobial agents and compounds have been performed in healthy volunteers and patients in stable conditions. Such studies have rarely been performed in critically ill patients, with multiple organ failure and capillary leakage and considerable co-medication, in whom these compounds are potentially life-saving drugs. This is the first study to demonstrate that the fixed drug preparation of pip/taz can be used safely and is suitable for initial treatment in critically ill patients in renal failure with CVVH renal function replacement. The continuation of treatment with this combination, however, requires a relative adjustment of the taz dosage or interval. Pip removal by CVVH is significant; the drug dosage should be as in patients with slightly impaired renal function. Taz clearance by CVVH probably does not significantly add to overall drug clearance. Taz should therefore be given as in anuric non-dialysed patients. The CI_T values, as calculated by two compartment pharmacokinetic fitting of the serum levels of taz and pip, were comparable to data published in the literature [10–13]. Schetz et al. [12] have given a theoretical model for drug elimination in continuous renal replacement therapy. In their paper, pip elimination would appear to be higher than in the paper by Sörgel & Kinzig [10] and in our patients, but data on taz elimination were not mentioned in the other reports [11–13]. To gain more insight into the relative contribution of CVVH in the CI_T of pip and taz, we calculated the CVVH ultrafiltrate rate during pharmacokinetic studies with the pharmacokinetically calculated CI_T of both compounds. For both compounds a statistically significant correlation was found. However, the calculated CI_T values were clearly higher than the CVVH ultrafiltration rates, indicating the existence of other routes of elimination. This study has not addressed the issue of relative drug clearance by CVVH versus total drug clearance – this would require a follow-up study with measurement of the drug levels in the ultrafiltrate.

Although no drug toxicity attributed to the treatment with pip/taz was noted in this patient group, and taz toxicity has not been described in the literature, we expect that accumulation of taz would have occurred if the

Table 2 Piperacillin/tazobactam pharmacokinetic values (MW/PHARM software) [9] (CI_T *V1, V2* total clearance, apparent volumes of distribution, assuming a two-compartment pharmacokinetic model)

	Piperacillin Value (SD)	Tazobactam Value (SD)
$t^1/_2$ (h)	5.9 ± 2.9	8.1 ± 3.7
CI_T (l/h)	2.52 ± 1.38	4.44 ± 2.28
(ml/min)	42 ± 23	74 ± 38
V1 (l/kg)	0.115 ± 0.081	0.251 ± 0.134
V2 (l/kg)	0.184 ± 0.125	0.287 ± 0.143

Table 3 Microbial isolates recovered from the patients studied (*R* resistant to growth, *S* sensitive, inhibition of growth in standard test, *B* bloodstream, *U* urine, *T* endotracheal aspiration (in mechanically ventilated patients))

Micro-organisms recovered	Number/site of clinical isolates	In vitro sensitivity
Escherichia coli	B (1) U (3)	S
Morganella morganii	T (1)	S
Streptococcus pneumoniae	T (1)	S
Streptococcus faecium	W (1)	S
Bacteroides faecalis	B (2)	S
Listeria monocytogenes	B (1)	S
Pseudomonas aeruginosa	T (2) B (1)	S
Stenotrophomonas maltophilia	T (2)	S
Serratia marcescens	U (1)	S
Citrobacter freundii	U (1)	S
Proteus mirabilis	U (1)	S
Enterobacter cloacae	U (1)	S
Staphylococcus aureus	T (1) skin (1)	S
Candida albicans	U (2)	R
Coagulase – negative Staphylococcus	B (3) skin (1) U (1)	R/S/S
Enterococcus spp	B (1) T (1) U (2)	S

measurements had been continued over a longer period of time, and possible subsequent untoward effects might have occurred if the treatment had been continued over longer periods of time. As the CI_T of taz seems to correlate with the CVVH ultrafiltration rate, levels may even rise further during prolonged periods of filter dysfunction.

As could be expected in this setting with severely critically ill patients with a wide variety of clinical diagnoses, drug serum levels showed a wide inter-patient variation. In clinical practice, however, the major concern is to avoid undertreatment with antimicrobial drugs with low toxicity profile, and we therefore chose to use a fixed drug treatment schedule. All serum levels measured in our patients appeared to reach levels well above the minimal inhibitory concentrations for all microbial pathogens isolated during the study period.

CVVH has gained considerable interest in the last few years among intensivists faced with patients with hemodynamic instability in need of renal function replacement therapy [13]. This method appears to be suitable for these patients, as it does not compromise, or depend on, the patient's hemodynamic reserve. Few studies are available on the pharmacokinetics of antimicrobial agents in CVVH-treated critically ill patients with renal failure. In many of these patients, renal failure is caused by potentially transient acute tubular necrosis on the basis of underlying severe sepsis. It is, therefore, critical to gain knowledge of the pharmacokinetics of antimicrobial drugs without intrinsic nephrotoxicity, to avoid further renal damage. It has been our policy to avoid aminoglycosides in the setting of sepsis complicated by acute tubular necrosis.

We conclude that pip combined with taz is a useful antimicrobial drug combination for critically ill patients requiring CVVH, that the fixed drug combination is suitable for initial management but that, on continuation, the fixed preparation carries the risk of increased accumulation of the taz component and that, during continuation, pip alone should be given intermittently with the pip/taz combination.

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